VOLUME 2 AUGUST, 1928 NUMBER 2

ANNALS OF INTERNAL MEDICINE

PUBLISHED BY

The American College of Physicians

CONTENTS

Issued Monthly

ANN ARBOR, MICHIGAN

ANNALS OF INTERNAL MEDICINE

OFFICIAL PERIODICAL OF THE AMERICAN COLLEGE OF PHYSICIANS

DEPARTMENT OF REVIEWS

The Journal will make an especial feature of the review of monographs and books bearing upon the field of Internal Medicine. Authors and publishers wishing to subject such material for the purposes of review should send it to the editor. While obviously impossible to make detailed reviews of all material, an acknowledgment of all matter sent will be made in the Department of Reviews.

Editor

Alfred Scott Warthin, M.D.
Pathological Laboratory, University of Michigan
Ann Arbor, Michigan

Price per volume, net, postpaid, $7.00, United States, Canada, Mexico, Cuba, $7.50 other countries

Entered as second class matter at the Post Office, Ann Arbor, Michigan

Individualization in Clinical Medicine*

By JULIUS BAUER, M.D., *Professor of Internal Medicine at the University of Vienna (Austria)*

MR. President, ladies and gentlemen: Before entering upon the subject of my convocation address I feel indebted to give you the assurance of my deep and respectful appreciation. It is a great honour not only to myself, but also to our old medical school of Vienna that one of its younger members was selected this year by the Board of Regents of the American College of Physicians to be its guest at the Annual Meeting and to deliver the Convocation Address. Concerning the subject of this address I thought it would meet with your approval not to talk about a too specialized and limited subject but to consider a problem of a more or less general medical interest. At the same time I thought you might expect to hear something connected with the research work I have been doing myself in the last fifteen years, that is with the physiology and pathology of the human constitution.

Among the medical profession and in the scientific discussion of general medical problems we have observed in Central Europe, during the last few years, something like a crisis. In medical journals and in medical societies the logical and philosophical basis of the medical profession is discussed; one likes to establish a sharp line of demarcation between the science of medicine itself and the doctor's medical art which is somewhat more than the pure practical application of a science. It is true, the new advances of our knowledge about the vital mechanisms in our organism in health as well as in diseases are remarkable. We have at our disposal almost innumerable physical, chemical, serological, biological methods and functional tests by which to elucidate a "case", and to construct a clinical diagnosis from all the symptoms and laboratory findings. But the more numerous these methods are, the more difficult is the thorough evaluation of their results, the more frequently a discrepancy between them will be met with. There is not always a parallelism between the number of routine-examinations performed in the laboratory of a clinic and the reliability and correctness of the clinical diagnoses on one hand, and the therapeutic results obtained by this clinic on the other hand. The reason for this is only in a small degree their insufficiency, and therefore the low value of a great number of all these methods and tests, but to a much greater degree it is due to the fact that a true diagnosis and a suit-

*Convocation Address, New Orleans meeting, March 9, 1928.

able treatment must be based, not only upon methods of a purely collective, or statistical value, but also upon the individual features of a case, upon the personal constitutional characteristics of an individual. The detection of these individual features, the most complete understanding of an individual patient's morbid condition, requires more than the pure evaluation of all possible routine-examinations, it requires a thorough knowledge of the patient's premorbid personality, of its constitutional characteristics including the psychical side which can not be separated from the somatic side of the organism.

A case under my own observation will illustrate better than many words what all this means and how such an individualization in the analysis of a patient's condition is to be understood and executed. I have under my care a surgeon's wife of about 36 who has suffered from gall-stones for many years. Typical colics, a marked tenderness after the attacks, and lately a positive cholecystography permitted this diagnosis with the high probability of nearly 100 per cent. The attacks were released as usually in this disease by a so-called dietetic error, particularly fat food and by psychical emotions. They came particularly at the premenstrual or menstrual period. So far the routine-diagnosis was easily established and as the usual internal routine-treatment did not bring any relief the operation was taken into consideration by the husband. But even if the mortality of an operation were not greater than 1 per cent—in gall-stone operations it is certainly higher—we have to remember the *"primus non nocere"* and we have to consider the possible consequences of a surgical treatment. Let us see what the individual analysis of the case revealed and what good resulted. The first important fact was here that there never were symptoms of an inflammatory process of a cholecystitis, and never symptoms of an obstruction of the bile duct. The subjective symptoms of the disease were only colics due to the spasm of the smooth muscles in the biliary tract. These spasms were released by the quite adequate stimulus of the foreign bodies in the gall bladder. But why did these calculi work as a reflex stimulus only at certain periods at certain intervals? Why can another individual have in his gall-bladder a great number of concretions for years and decades without having a notion of this pathological condition? It was the famous German surgeon Riedel who considered that approximately 95 per cent of all carriers of gall-stones never suffer from that condition. Only 5 per cent would be really ill on account of colic or inflammatory complications. The spasm of the biliary system is released by the concretions—it is true—but only in certain individuals and in our patient only at certain periods, obviously only when the threshold of the nervous irritability was particularly low. Our patient had without any doubt generally a low threshold for nervous stimuli, she was a very sensitive, irritable, nervous person with hereditary marks of a biological—not social—inferiority of the central nervous system. She, and the whole family were of unusual intelligence, but one brother died of a brain tumor, another is a psychopathic

degenerate. The patient as well as her father and her daughter react with delirium to occasional febrile diseases. She had gray hair at the age of 25. Psychical emotions diminish the nervous threshold just as the menstruation does and both are the factors that release the attacks. Concerning the third factor, the dietetic errors, it was easy to establish that the psychic factor rather than the alimentary was the active moment. The fear of getting a colic after a forbidden food was proved experimentally in our case to release attacks whilst the formerly forbidden dish itself had lost this influence after informing the patient as to the neuro-psychical mechanism of the colics. She was fond of mayonnaise, for instance, and ate it sometimes at a social party in spite of it being forbidden by her physician. A gall-bladder colic in the following night was the regular consequence. But the patient could tolerate without the slightest trouble a mayonnaise after she was informed that not the mayonnaise itself, but the consciousness of having eaten something harmful and the fear of an attack was the cause of the colic. It is obvious that the schematic, not individualized, dietetic routine-treatment had harmed our patient more than it had helped her. The simple explanation of the situation and the calming influence of my talk was sufficient to suppress any disorders due to the gall-stones for 8 months. At this time a new colic came immediately after hearing a gentleman's minute description of his own gall-bladder operation which he gave to his neighbour at a social party. I must beg your pardon to have related a simple case of gall-stones so much in detail, but it is representative of many hundreds of similar and analogous cases not only of gall-bladder trouble but of other conditions as well. It shows that the usual diagnostic label gained by the routine-examinations and put on a case is not quite sufficient, and that we have to proceed beyond the diagnosis of a disease to a thorough analysis of the individual patient in order to complete our conception of what happens in the patient's organism, and in order to raise our therapeutic effects to the highest possible level.

Something of prime importance is illustrated by our patient. She *had* gall-stones and *suffered* from a nervous condition closely related to this organic abnormality. There was not a bit of what we may call hysteria or neurasthenia. Nobody will call this condition a neurosis in spite of the undoubted effects of psychical treatment. It is just a simple case of gall-stones, but it exemplifies that we are quite wrong to separate sharply organic and functional, nervous and psychogenic disorders, that we are wrong to neglect the little psychotherapy of many organic diseases and to say: either internist or psychotherapist. Always *"et-et,"* always somatic *and* psychic treatment at the same time and in the appropriate dosage and relationship. It is *individualization* in the diagnostic analysis beyond the diagnosis of the disease, and it is *individualization* in the treatment that we want.

In the last few years we have learned by clinical and psychological studies that somatic and psychic processes are so closely connected with each other that we have to deal with a psycho-

able treatment must be based, not only upon methods of a purely collective, or statistical value, but also upon the individual features of a case, upon the personal constitutional characteristics of an individual. The detection of these individual features, the most complete understanding of an individual patient's morbid condition, requires more than the pure evaluation of all possible routine-examinations, it requires a thorough knowledge of the patient's premorbid personality, of its constitutional characteristics including the psychical side which can not be separated from the somatic side of the organism.

A case under my own observation will illustrate better than many words what all this means and how such an individualization in the analysis of a patient's condition is to be understood and executed. I have under my care a surgeon's wife of about 36 who has suffered from gall-stones for many years. Typical colics, a marked tenderness after the attacks, and lately a positive cholecystography permitted this diagnosis with the high probability of nearly 100 per cent. The attacks were released as usually in this disease by a so-called dietetic error, particularly fat food and by psychical emotions. They came particularly at the premenstrual or menstrual period. So far the routine-diagnosis was easily established and as the usual internal routine-treatment did not bring any relief the operation was taken into consideration by the husband. But even if the mortality of an operation were not greater than 1 per cent—in gall-stone operations it is certainly higher —we have to remember the *"primus non nocere"* and we have to consider the possible consequences of a surgical treatment. Let us see what the individual analysis of the case revealed and what good resulted. The first important fact was here that there never were symptoms of an inflammatory process of a cholecystitis, and never symptoms of an obstruction of the bile duct. The subjective symptoms of the disease were only colics due to the spasm of the smooth muscles in the biliary tract. These spasms were released by the quite adequate stimulus of the foreign bodies in the gall bladder. But why did these calculi work as a reflex stimulus only at certain periods at certain intervals? Why can another individual have in his gall-bladder a great number of concretions for years and decades without having a notion of this pathological condition? It was the famous German surgeon Riedel who considered that approximately 95 per cent of all carriers of gall-stones never suffer from that condition. Only 5 per cent would be really ill on account of colic or inflammatory complications. The spasm of the biliary system is released by the concretions—it is true—but only in certain individuals and in our patient only at certain periods, obviously only when the threshold of the nervous irritability was particularly low. Our patient had without any doubt generally a low threshold for nervous stimuli, she was a very sensitive, irritable, nervous person with hereditary marks of a biological—not social—inferiority of the central nervous system. She, and the whole family were of unusual intelligence, but one brother died of a brain tumor, another is a psychopathic

degenerate. The patient as well as her father and her daughter react with delirium to occasional febrile diseases. She had gray hair at the age of 25. Psychical emotions diminish the nervous threshold just as the menstruation does and both are the factors that release the attacks. Concerning the third factor, the dietetic errors, it was easy to establish that the psychic factor rather than the alimentary was the active moment. The fear of getting a colic after a forbidden food was proved experimentally in our case to release attacks whilst the formerly forbidden dish itself had lost this influence after informing the patient as to the neuro-psychical mechanism of the colics. She was fond of mayonnaise, for instance, and ate it sometimes at a social party in spite of it being forbidden by her physician. A gall-bladder colic in the following night was the regular consequence. But the patient could tolerate without the slightest trouble a mayonnaise after she was informed that not the mayonnaise itself, but the consciousness of having eaten something harmful and the fear of an attack was the cause of the colic. It is obvious that the schematic, not individualized, dietetic routine-treatment had harmed our patient more than it had helped her. The simple explanation of the situation and the calming influence of my talk was sufficient to suppress any disorders due to the gall-stones for 8 months. At this time a new colic came immediately after hearing a gentleman's minute description of his own gall-bladder operation which he gave to his neighbour at a social party. I must beg your pardon to have related a simple case of gall-stones so much in detail, but it is representative of many hundreds of similar and analogous cases not only of gall-bladder trouble but of other conditions as well. It shows that the usual diagnostic label gained by the routine-examinations and put on a case is not quite sufficient, and that we have to proceed beyond the diagnosis of a disease to a thorough analysis of the individual patient in order to complete our conception of what happens in the patient's organism, and in order to raise our therapeutic effects to the highest possible level.

Something of prime importance is illustrated by our patient. She *had* gall-stones and *suffered* from a nervous condition closely related to this organic abnormality. There was not a bit of what we may call hysteria or neurasthenia. Nobody will call this condition a neurosis in spite of the undoubted effects of psychical treatment. It is just a simple case of gall-stones, but it exemplifies that we are quite wrong to separate sharply organic and functional, nervous and psychogenic disorders, that we are wrong to neglect the little psychotherapy of many organic diseases and to say: either internist or psychotherapist. Always *"et-et,"* always somatic *and* psychic treatment at the same time and in the appropriate dosage and relationship. It is *individualization* in the diagnostic analysis beyond the diagnosis of the disease, and it is *individualization* in the treatment that we want.

In the last few years we have learned by clinical and psychological studies that somatic and psychic processes are so closely connected with each other that we have to deal with a psycho-

physical unity. Almost every morbid condition is to a certain extent a psychophysical problem and its elucidation requires a detailed individual somatic and psychic examination, reaching farther than the statement of a usual clinical diagnosis of a disease. The clinician must have in his mind every moment, more than is usually done, the important laws of physiology concerning the facilitation of reflexes and particularly the so-called conditional reflexes. A reflex mechanism, as coughing or vomiting, may appear during an organic disease as a rather suitable and useful help for the organism. It is mobilized by the ill organism as a sort of adaptation in order to facilitate the vital conditions during this disease and to favor the reparation. But each time, when this reflex mechanism is activated, the threshold for the afferent nervous stimulus of this reflex is lowered. The more frequently the reflex is used the easier it may be released the next time and finally the releasing stimulus becomes not an adequate one any more, the reflex is released periodically by an accumulation of quite physiological stimuli; that means it becomes automatic, spontaneous and has lost entirely its original significance. It is easy to understand that such an automatization of reflex mechanisms is particularly to be seen in primarily nervous and irritable persons and that it is favoured by physiological moments, as hypochondriac anxiety or other related ideas. How frequently do we observe such prolonged automatized nervous cough in children after a whooping-cough, in adults after a simple catarrhal affection of the trachea or the bronchi, how frequently do we see vomiting patients who got accustomed to this prepared reflex by an acute dyspeptic trouble or even by a chronic peptic ulcer, by gall-stones or another organic abdominal condition. The hyperemesis gravidarum, the dysmenorrheic cramps and many other pathological conditions are to be understood only on the basis of the physiological law of facilitation of reflexes by their own activation.

Of an even higher importance for the clinical medicine are the so-called conditional reflexes. We owe to Pavlow the exact knowledge of the typical mechanism: If an event happens to coincide frequently with the activation of a reflex, then this event itself may acquire the power of the originally releasing stimulus. All that needs no further explanation before this forum. I remind you only of a well-known experience concerning a case of an anaphylactic bronchial asthma with a hypersensitiveness towards the odor of roses. The patient got an asthmatic attack when he was shown an artificial rose of paper. The optic impression of a rose so frequently coincided with the releasing action of the antigen that it gained the power to act as a releasing factor itself without the original antigen. It is obvious that this mechanism of conditional reflexes plays an important rôle not only in cases of asthma, but also in other pathological processes and that only a careful investigation of the individual can reveal the real situation. I had under my care a famous actress who complained of vomiting before playing a certain part. I could easily detect the mechanism of a conditional reflex. My patient had played just this special part with

great success abroad when she became surprised by a pregnancy with the physiological vomiting. The pregnancy was interrupted but the whole adventure was so effectively accentuated that the playing of this special part became charged with the power of a releasing factor of vomiting.

We internists must not overlook how far the influence of mental processes upon the body may go. Experiences of the last few years illustrate this fact sufficiently. Particularly do hypnosis experiments show that many somatic functions and important physiological acts may be influenced and regulated more by an individual's subjective visional world constructed with the help of a hypnotic suggestion, than by the real environment and by the usual real adequate factors. So it is possible to produce just the same changes in the blood following physiologically the intake of a greater amount of liquid by the pure hypnotic suggestion of drinking (Marx, Schilder and *myself*); we could find the same involuntary reactions, the typical pass-pointing of the hands, if we gave the hypnotic suggestion of being rotated, as after a real rotation of the body. Even the glycosuria and the blood sugar can be diminished by the pure suggestion of an insulin-injection during a deep hypnosis (Gigon). The most interesting experiment of this sort has been related by Hansen and Gessler of Krehl's clinic in Heidelberg. It is old knowledge, that a cooled organism wants more oxygen in order to adapt itself to the lower temperature by increased burning. So it was established that at a temperature of 59°F. the basal metabolism was increased about 18%, at a temperature of 54° F. about 30%. But cooled persons failed to raise their oxygen consumption as soon as they got the hypnotic suggestion of being in a warm room. On the other hand the basal metabolism rose markedly if the hypnotized person sitting in a heated room was given the suggestion of feeling chilly or of lying undressed in the snow. These experiments seem to be of a far-reaching importance. They demonstrate as clearly as possible that even quite involuntary and unconscious adaptative processes as metabolic functions get rid of the influence of physiological regulatory mechanisms as soon as these mechanisms are not in accordance with the subjective, imaginary situation. The visionary situation governs, the real environment may succumb if it is in contrast to the suggested fiction. The somatic machinery is regulated more by inside-influences than by outside factors if the normal conformity between the subjective and the objective situation is disturbed. Although we have not to deal in practice with complete analogies of the hypnosis experiments, except perhaps certain psychoses, we must always take into consideration the immense influence that psychical factors have upon somatic functions, so that even some of the usual laboratory findings may be modified by emotions, feelings and ideas which are not always recognized and registered by the physician. In addition we must remember how far the psychic side of a patient is influenced by the somatic. The humor, the frame of mind, the mental tonus, is dependent to a high degree on the body and so there may result more fre-

quently than one expects a vicious circle of a psycho-somatic disturbance which has to be understood and considered by the experienced physician.

We were taught to recognize disturbances of the human machinery and how to improve or to repair them. And this is quite right. But we must not forget, that it is not always an organic disturbance of the machinery itself that brings the patient to the doctor. Frequently he comes on account of unpleasant sensations, due to his organic disturbance only to a certain extent, and in part due to the patient's inclination for such a sort of feeling. What one person does not even notice may bother another extremely, particularly if a psychical repercussion is associated with the sensations. He who intends only to influence and to repair the disturbed machinery and does not care for this individual point of psychical repercussion is not a far-seeing physician, at least he does not make use of all opportunities of therapeutical results. It may be that in such a case a quack helps the patient better than the doctor, although he does not care at all for the defect of the machinery because he can not even understand it. It is harsh and disagreeable, indeed, to say these words before the profession, but first the truth must be recognized and accepted in order to fight against the error. Some examples may illustrate this situation.

Not infrequently we see in our office patients affected with a well compensated heart lesion complaining of palpitation and unpleasant ill-defined heart sensations. These sensations are often due to the increased attention paid to the heart by the patient on account of his knowledge of the valvular defect. The affective participation is quite a natural consequence and any treatment directed towards the fully compensated lesion is not only superfluous but even harmful because of its bad influence upon such a patient's mental attitude. A simple explanation and calming of these persons will help them. How frequently do we meet with enteroptotic asthenic nervous women whose troubles are not due to the ptosis of their kidney, colon or stomach, or to the retroflexion of their uterus, but are due to the consciousness of something wrong, something ptotic or displaced in their abdomen. This information given them by a physician increased, or even initiated, their unpleasant sensations. Therefore it is of the greatest importance to know that such a ptosis of the stomach, colon, kidneys and so on may be a constitutional characteristic of many thin, frequently asthenic, and almost regularly nervous persons. The same ptosis may be found during the whole life but the subjective troubles are only temporary and quite independent of the degree of the ptosis. The diagnostic label "enteroptosis" is frequently erroneous because it indicates only a constitutional type and does not touch the real mechanism of the complaints.

Quite a separate chapter are the hypertension patients. It is by no means exceptional to reveal a marked arterial hypertension as a purely accidental finding in persons who are examined thoroughly without showing any subjective symptoms of their vascular condition. For the patient it

may be quite a critical moment of his life to hear now about his arterial hypertension and to get prescriptions and advices concerning his future life. If he had felt perfectly all-right up to the moment of this consultation, he may become a broken man after that time and may live as a *wreck* the rest of his life, interested chiefly or exclusively in his blood pressure. Besides that this increased blood pressure may not even show a tendency to react to the different treatments. We must conclude that the routine-treatment directed against the disturbed machinery solely, that is against the hypentension, did not only fail entirely but was the cause of serious subjective disorders. We have to take into consideration and to check up before any information and treatment of a patient, the seriousness of the disturbance of his machinery, the probably repercussion on his psyche and the value of our prescriptions and advice.

Perhaps we are too circumstantial in discussing the highly important psychical side of the problem of medical individualization, and if we turn our attention to other questions related to this problem, we may use the example of hypertension first in order to illustrate a principal point. Why do we meet with an entirely different symptomatology in different cases of hypertension? The same anatomical and functional condition, the same degree of arterial hypertension may produce shortness of breath or aortalgia in one person, headache or dizziness in another, rheumatic pain in a third and may not bother at all a fourth. It may kill one patient by an apoplectic stroke, another by an insufficiency of the hypertrophied left ventricle with the subsequent lung edema and a third by a renal insufficiency and the subsequent uremia. The individually different progression of the anatomical changes in the small arteries, the individually different involvement of special parts of the peripheral blood vessels, the individually different reactivity and resistance of the heart muscle and the varying tendency of the overdistended arteries to spastic contractions in different parts of the body are to be considered as the chief causes of the variability of the clinical picture of the genuine permanent arterial hypertension. The physician who watches carefully the family history of his patients will be convinced that constitutional factors are here of undoubted influence. Sometimes we may meet with particularly interesting mechanisms explaining the special symptomatology of an individual case. I was consulted once by a gentleman of 54 on account of a constant slight dizziness which was certainly to be attributed to a moderate hypertension of 180. No other symptoms were to be found except a partial deafness of the right ear. The man had suffered since his 18th year from typical fits of Ménière in rather long intervals due to the lesion of his ear. His mother and sister suffered from migraine. It seems probable that the involvement of the static apparatus in the widest sense by the Ménière's disease was the determining factor of the special symptomatology of the beginning hypertension. The old Ménière facilitated the sensation of dizziness now provoked by the arterial hypertension. It was a sort of facilitation which prepared

this particular clinical picture of hypertension.

Everyone is familiar with the rather various clinical forms of heart decompensation. A great many of these individual differences are due to the different involvement of the right or left part of the heart and are easily explained by purely mechanical factors. It was particularly Wenckebach of Vienna who pointed out, how the prevailing congestion of the lungs or of the liver included the portal circulation, how in other cases the predominant congestion in the cava superior may be explained by mechanical factors only. In spite of this statement we have to acknowledge the observation of Kretz, Jr., of Vienna concerning the different reaction of thin, asthenic people and broad-shaped, rather well nourished, pyknic individuals upon a heart decompensation. The first group, the longitudinal type, has generally a greater tendency to congested and prominent veins, to cyanosis, to liver- and lung-congestion, to embolism and hemorrhage, but is not inclined to edema; the second, the broad, lateral type, shows the very opposite reaction, the tendency to edema and to dropsy of the great body cavities. There is no doubt about the individually different tendency of the tissues to develop edema. The avidity for water is certainly greater in a skin containing a considerable layer of subcutaneous fat. We meet with this coincidence of fat and of water avidity of mesenchyma also in a quite different pathological condition, that is in certain cases of lipomatosis. I saw recently a case of otherwise well compensated mitral insufficiency with a very obstinate slight edema of the legs, disappearing after a night's rest but being present in upright position for many years in spite of all treatments and a rather sufficient digitalization. The patient, a lady of about 45, had at the same time a moderate and localized lipomatosis of the legs which was even more striking in her sister and niece. This constitutional characteristic determined the extreme disposition to the development of cardiac edema.

One of the most interesting examples pointing towards the necessity of individualization is the condition called hemolytic anemia or hemolytic jaundice. Usually one separates two types of this disease, a congenital and an acquired. That is wrong in my opinion. Even the apparently acquired cases are, according to my own observations, constitutional, although latent up to the moment of the action of a releasing factor, as pregnancy, syphilitic infection and so on. They were latent by compensation and became manifest by an insufficiency of the over-strained compensating organs. In the families of those patients we may find by chance individuals who feel perfectly healthy but show definite signs of their constitutional abnormality. One of these practically healthy family-members may show a markedly decreased osmotic resistance of his red blood corpuscles with or without an enlarged spleen, another may show a considerable hyperbilirubinemia and urobilinuria, a third an aniso- and microcytosis of his blood. All these individuals need not have any anemia or jaundice as long as the bone marrow and the liver are sufficiently compensating the precipitate

blood moulting. But they have to work harder in such a person whose erythrocytes live a shorter time than normals because of their premature destruction in the spleen and liver. All our organs work at a certain optimum and possess a reserve power of an individually different degree. If they are overstrained to the maximum of their reserve power then the insufficiency, and consequently the functional disturbances of the machinery, are inevitable. In this instance it is the biological value and the adaptative power of the bone marrow on one side, and of the liver on the other side which decide whether such an "hyperhemolytic" individual, if I may use this term, lives healthy without disorders or whether he develops a hemolytic anemia or a hemolytic jaundice. What we may find in such a compensated case, the enlargement of the liver or of the spleen, the low osmotic resistance of the red blood corpuscles, the hyperbilirubinemia or urobilinuria are not yet symptoms of a disease but are indicators of a constitutional deviation bearing upon the physiological "moulting" of the red blood cells. These individuals are not ill, but they are highly disposed to develop the illness at a most trivial occasion or spontaneously by an exhaustion of the overstrained organs.

To discuss the problem of individualization in cases of tuberculosis is almost impossible, but it seems rather superfluous as every experienced physcian knows about the striking individual differences in the clinical picture, in the outcome and the effects of the applied treatment. These differences are not only due to the infection with different strains of bacilli or to their different quantity and virulence, but they are also to be attributed to the various culture media presented by various individuals. I had a patient suffering from a lupus vulgaris and affected with a pathological obesity. The tuberculous infection came without any doubt from the father who was suffering, as well as his brother and sister, from a chest tuberculosis. These three persons were thin and had a longitudinal, asthenic habitus. The father infected two of his children, but no one developed a pulmonary condition, one had a lupus, the other lymphomata colli. All children had inherited the mother's habitus and were, just as the whole mother's family, extremely stout. A body weight of 200-300 lb. was the rule among these people. May one deny that the Koch bacilli growing in the father's lung grew differently in the entirely different culture medium of the obese race? They did not affect the chest but other organs of this race. Can it be a pure accident, if the American urologist Kretschmer describes a renal tuberculosis in identical twins, girls 14 years of age? Only the identical bacterial culture medium of the identical constitution can explain satisfactorily this striking coincidence of a not at all frequent condition.

The most important rôle played by the individual constitution is in endocrine disorders. Many of the frequently alleged endocrine symptoms are to be attributed to a primary constitutional anomaly of this very individual and have nothing to do with the endocrine glands, or at least they are not due wholly to endocrine disorders.

I had the honor to point out more in detail some of these highly interesting questions 4 years ago in this country, and my address has been published in the American Journal of Endocrinology of 1924. It would go too far to discuss that to-day anew and I will confine myself to drawing your attention only to the most different symptomatology of one and the same endocrine disturbance in different individuals. It needs no further discussion that the same degree and sort of thyroid insufficiency may produce in one man a marked psychical sluggishness and nervous disturbance, in another a marked anemia or the typical skin changes, in a third an obstinate constipation, or serious so-called rheumatic pain, in a fourth heart trouble or a progressive obesity. In the moderate, oligosymptomatic cases the arrangement of hypothyroid symptoms is individually different. If the lack of thyroxin is a complete, or nearly complete one, then each part of the organism will show the typical features of the insufficient supply of the hormone. If the lack of thyroxin is only partial then the consequences of the insufficient hormonization will become manifest in a various degree in different organs. Some organs will show their insufficient hormonal regulation earlier and more than others. That depends on the individually different constellation of the biological value of the organs, whether an organ or a special function requires more, or less, of the hormonal stimulus or whether it is secured by its own autochthonous mechanism. I spoke of a "principle of multiple safety" governing the function of our organs. They are secured by their own structure and "Anlage", but they are secured also by a hormonal and by a nervous regulation. The various degrees of each of these three safety mechanisms explain the various clinical picture in oligosymptomatic, that is partial, endocrine disorders.

What is true for the thyroid insufficiency is true also for the hyperthyroid conditions. The leading symptoms of these oligosymptomatic cases may vary considerably. At one time it is tachycardia and palpitation, at other times tremor and nervousness, even psychical disturbances, or serious vasomotor symptoms, at other times diarrheas, and dyspeptic disorders, or it may be a rapid loss in weight, or a glycosuria which induces the individual to consult a physician. Quite a different clinical picture, but an identical causal factor, one and the same hyperthyroidism! The different individual reactivity of the peripheral organs upon the exaggerated hormone-supply is due to their different biological value and the safety mechanism of their function. We can observe regularly that individuals with predominant heart symptoms in a hyperthyroidism originate from a sort of heart-family where other members suffer from other heart conditions, we see patients with hyperthyroid diarrhea originating from gastro-intestinal families and so on. In any event, the clinical picture of all these incomplete endocrine disorders is never dependent upon the glandular lesion alone but always also upon the individual constitution with the consequently various hormonal reactivity of the organs.

We meet in practice with all borderline cases from the complete defi-

ciency, or the most extreme abundance of the hormone to the normal condition, from the classical clinical pictures through the rudimentary, oligosymptomatic cases to the normal. In this way we may see once in a while a case which we may designate as monosymptomatic, as, for instance, a simple tachycardia or a constipation which is considered as a monosymptomatic form of hyper- or hypothyroidism. But this assumption does not seem logical. In a pure monosymptomatic endocrine case where only one single symptom would betray the endocrine anomaly, it is practically not the endocrine function which is altered, but it is reactivity of one single organ upon the hormone; because the amount and quality of this hormone is obviously appropriate for the requirement of all other organs and is apparently insufficient or exaggerated only for the single organ giving rise to the term monosymptomatic endocrine disorder. We see, therefore, that monosymptomatic endocrine disorders are not to be acknowledged, they do not exist actually, and we meet with the greatest difficulties of classifying some special clinical cases according to the rôle played by the endocrines, by the vegetative nervous system and by the organs themselves in the production of pathological symptoms. Only a thorough examination and individual analysis of the case, with reference also to the family history, will help us to understand the pathological mechanism and will prevent us from the most disgusting abuse of the endocrine glands in a pseudo-explanation which seems to be satisfactory but is only modern. Individualization is indispensable also in this field of clinical medicine and we must take into consideration the psychical side of a patient just as at any other time.

I am afraid that my talk has tired you since you have heard nothing new but only old and well-known facts, at least known to you through your own practical experience, if not through your medical studies. It is true, there *is* a difference between the pure medical science and the art of its practical application at the patient's bedside. This art is somewhat more, indeed, than this application only, it requires more than a complete knowledge of all scientific details, it is and will be always an art which never will be transformed into an exact science, as the complete understanding of one person's psychophysical machinery never will permit us to understand a second man's personality just as well by a pure analogy, because of the practically infinite variability of the individual constitution. The individual analysis must start always anew, and what science of the human constitution may help, is only to establish certain groups of more or less pronounced common characteristics in somatic structure, in physiological and pathological functions, in the reactivity to exogenous and endogenous stimuli and disorders; but it will never replace entirely the doctor's art to reveal the individual particularities of his patient and to take them into consideration in analyzing the pathogenesis of a patient, in constructing his diagnosis and in applying the fitted treatment. The medical *science* must be and will remain always the indispensable solid basis of a doctor's art, but this medical *art* must be the aim of the profession and the aim of medical education.

A Review of Research in Yellow Fever*

By Aristides Agramonte, M.D., *University of Havana, Cuba*

WHEN we contemplate, in our present security from yellow fever, all that has been suffered by other communities, none less than this one of your beautiful city, in the terrible days now fortunately past, but which extended even to our present generation; when we realize the incalculable number of lives that have been preserved through the conquest of that scourge; when we look about us and observe the material progress that has been attained by the apparently simple fact that we can prevent the occurrence of epidemics; when we visit the Panama Canal and remember that it was made possible only through a proper sanitary control during its construction, and how Vera Cruz, Havana, Rio de Janeiro, Guayaquil and other cities have become, not only perfectly habitable by the white man, but in some instances, as in the case of my own city, (Havana,) they well deserve now to be considered as health resorts; when we realize all these things, we cannot help but become appreciative of the value of the work which those who have gone before us undertook and carried out so successfully.

*Read before the American College of Physicians, Annual Clinical Week, March 9, 1928, New Orleans, La.

The origin of this malady has been the subject of much learned discussion and deserves that we consider it, if only very briefly, inasmuch as the most active and effective investigations have been undertaken in America.

If we leave out of consideration the equivocal Maya writings and the exaggerated and often visionary histories provided by the Spanish adventurers and colonizers of the XV Century, as I am inclined to do, if we compare the period at which the indisputable epidemics of yellow fever did appear in this hemisphere with other contemporary circumstances, we cannot but remark that only after the introduction of the black slave trade, did yellow fever became evident amongst any white population. Investigation carried out in our present century, has shown that it was not unknown along the West coast of Africa, we can hardly presume for how long, until it was clearly pointed out by Robert Boyce, of the Liverpool School of Tropical Medicine, in 1910; since then, several perfectly well-defined epidemics have been described and a focus of endemic yellow fever has been demonstrated there; it is evident that the disease is maintained among the blacks endemically, exploding in epidemic form at irregular periods among the comparatively few white inhabi-

tants, making thus an immune element from those who survive and repeating the process when there is a new influx of non-immune residents in the towns. The isolated condition of that part of the world, with relation to the countries inhabited by a white population and the total absence of emigration from West Africa to European or other states, has probably been the reason why our attention had not been directed to those parts as a possible source of yellow fever, until the last twenty years.

From the time that it became implanted in the West Indies, as an importation, be it from the mainland or from Africa, it remained there for fully two and a half centuries, serving as a constant menace to other territories in America and in Europe. The cities of Havana, Vera Cruz, Panama, Guayaquil and Rio de Janeiro became well-known plague spots and were shunned by travel and trade, as much as possible, during the summer months. From them and from the Lesser Antilles which were practically neglected from a sanitary standpoint, the disease traveled North and South; only seventeen years after the settlement of Philadelphia, (1699,) it was visited by a yellow fever epidemic; more dreadfully in subsequent years, (1741, 1747, 1762,) each time certainly imported from the South, (Charleston and other towns that had been invaded from the Caribbean Islands,) but in the year 1793 the appearance of the disease was accompanied by such a mortality that it carried panic into the homes and caused a great exodus from the city; in the short space of a month and a half, more than 4,000 deaths occurred in a population of 40,000 people. The first half of the XIX Century was particularly rife in yellow fever epidemics, extending over the widest territory that it has been known to cover till then and since then; it spread from America to southern Spain, to some ports of France, to Leghorn, Italy, and the southern United States. While in all these places the epidemics were regularly terminated with the advent of autumn and winter, the disease smouldered uninterruptedly in the Caribbean and Gulf coasts of America throughout the year. The sanitary history of your own city during the last century is a salient example of what woe and misery always attended the invasion of a non-immune community by this disease.

The number of lives sacrified to our ignorance of its epidemiology and etiology, certainly reaches to many hundred thousands; there are not very clear records from the French and Spanish possessions, but those of cities along the Atlantic coast and the Mississippi valley show that the figures above quoted are not exaggerated. The amount of money it has cost through loss of life, interruption of business and trade and unnecessary expense, if it could be calculated, would be found to be many millions of dollars.

In truth, my subject does not deal directly with these matters, but it is important that we keep them in mind, better to appreciate the blessing of immunity we now enjoy and the happy future that we dare to foresee and foretell.

Naturally, during the earliest period in the history of yellow fever, the most

prominent physicians of the time, particularly of the regions affected, became intensely interested in its investigation; however,this was necessarily limited to a study of the symptomatology, a comparison with alleged similar conditions or diseases and the consideration of numerous hypothetical questions as to its sources and methods of transmission. A glance over the literature, which is astonishingly vast, reveals wonderful sagacity, power of observation and deduction on the part of many practitioners not otherwise renowned. The names of DuTertre, Rush, Caldwell, Massie, Chervin, LaRoche and many others forming legion, appear in exhaustive papers and monographs pertaining to the study of this disease; their activities were restricted to personal observation of cases, detective functions tending to discover the hidden method of their dissemination, depending greatly on hearsay information from very unreliable sources, resulting in their work, on the main, in a series of generally erroneous presumptions and theories. Important factors in misleading the most painstaking and earnest investigators were, undoubtedly, the belief in spontaneous generation, in the action of mephitic air or miasms, in the noxious influence upon the atmosphere of accumulated excreta, in the action of poisonous gases evolved from the bilge water of ships, to say nothing of the influence superstitiously attributed to the heavenly bodies.

Until the later part of the XIX Century, investigators were deprived of the aid of laboratory or experimental facilities; in fact, it was with the birth and development of bacteriology that the first attempts at a really scientific research were made.

For the purpose of this address, I have divided the subject matter into two periods; the first, embracing the last quarter of the last century, and the second, from the year 1900 to the present date, taking in review the principal attempts and failures and the reasons for them, and the successful efforts of the more recent investigators.

Alas! the failures far surpass the successes, but each in its own way carries a lesson that we might profit by, and if as yet we have not been enabled to grasp the elusive parasite, that seems not to be of paramount importance if our aims tend, as they should, by all means to the extirpation of yellow fever from the earth, and I feel that we should be much elated at the present outlook, the disease having virtually been driven to its last redoubt, upon the western coast of the Dark Continent.

The Period Previous to 1900

It is rather unfortunate that some of the men who have worked in an attempt to elucidate the problems connected with yellow fever, its etiology and propagation, were not always inspired primarily by the desire to discover the truth and thus contribute to the welfare of humanity; when we closely scrutinize the claims and the announcements of these men, we are sorry to find that even some few who enjoyed high prestige among their fellow citizens, upon more than one occasion, directed their labors and their results to their own benefit. In this respect, the work of the last century

was very unlike that carried out during the present one in which the investigators expected no material reward for their labors, having performed them in the line of duty; and the millions that have been spent from public as well as private funds were used so exclusively in carrying out laboratory and experimental research and such general sanitation as will probably cause in due time the total extinction of yellow fever.

From the year 1880 to 1887, Dr. Domingos Freire, in Rio de Janeiro, Brazil, was engaged in applying what might have been considered then as modern bacteriologic methods in his investigation of yellow fever and finally claimed to have found the cause of the disease in an organism presumably isolated from the blood and tissues of such cases, which organism, after due (and probably secret) manipulation could be employed to immunize susceptible individuals. The statistics presented to back up such assertions were very encouraging.

From a careful study of the methods employed and the trend of Dr. Freire's investigations, it is evident that he had in mind, to the exclusion of every other thought, the finding of some micro-organism that would answer to what he believed were the requirements of the yellow fever germ. He had limited his investigations to obtaining cultures, but no further study was made of them, nor of the tissues from which they were at times obtained. The tubes containing them he even took to Europe in an effort to secure scientific sanction from the bacteriologists of that time. The organism, supposed to have been uniformly isolated from cases and cadavers of yellow fever, upon investigation proved to be the common staphylococcus albus; it in no way corresponded to the descriptions made of the Cryptococcus xanthogenicus. But the worst aspect of all the story connected with this scientific swindle rested upon the fact that by means of a supposedly attenuated strain, vaccinations with this organism were practiced in a large scale upon the non-immune population. The Brazilian Government went to the extent of appropriating funds for the preparation and application of the yellow fever vaccine; learned and scientific bodies heaped honors upon the instigator of this fraud, while people continued to contract the disease and the same proportion as before the inoculations, died of it.

Major Geo. M. Sternberg, U. S. Army, having been detailed for the purpose, after careful investigation says:

"Having reviewed at length the claim of Dr. Domingos Freire to have discovered the specific germ of yellow fever and to have transmitted this disease to certain lower animals by inoculation, and having arrived at the conclusion that these claims are without scientific foundation, it may be thought that no further demonstration is required in order to show that his protective inoculations are without value. The inoculations practiced are said to be made with cultures containing the attenuated microbe of yellow fever; *a priori* it would appear that if there has been no veritable discovery, and if there is no sufficient evidence that the cultures used contained the

specific germ of yellow fever, no value can be attached to such inoculations."

This practically put an end to Freire's claim, but with the notoriety obtained and the aid of influential friends in the government of his country, the preventive inoculations continued for some time and the inventor waxed rich and prominent.

At the same time that the Freire hoax was being perpetrated in Brazil, (1885-1887,) another investigator, in Mexico, was putting forth a similar claim, affirming that he had discovered a definite and specific organism in the blood and urine of yellow fever cases. It is curious, in connection with this work, that Dr. Carmona y Valle never obtained the material himself, but had it brought to him from quite a distance, by his associates.

The cultures which he presented to Dr. Sternberg, who having finished with the Freire investigation went after this Mexican claim, contained both a micrococcus and a bacillus. When asked about this peculiar symbiosis, Dr. Carmona explained that his idea was that the micrococci were "zoospores" which subsequently germinated in the form of bacilli and that the latter, in time, broke up into spherical bodies. The persistence of brownian movement in the so-called "zoospores" was to him sure proof of their great vitality and resistance to destructive agencies. These fallacious results could not withstand the careful scrutiny to which they were subjected and their worthlessness was soon demonstrated.

Dr. Carlos J. Finlay, of Havana, in 1881, as we shall see later, announced his theory that yellow fever was transmitted from man to man by the bites of mosquitoes. Imbued with the spirit of bacteriological research that dominated at the time, with reference to infectious diseases, he undertook, with the assistance of Dr. Claudio Delgado, who had acquired some laboratory training abroad, to obtain cultures of such organisms as might be accused, more or less justly, of being the yellow fever parasite. In the years 1886-1887, these investigators gave as a result of their work a tetracoccus, (micrococcus tetragenus versatilis, Sternberg,) and probably other tetracocci in plantings made from finger blood, blister serum and secretions, (tears, urine, etc.) of yellow fever patients.

Inasmuch as five years before, Dr. Finlay had indicated that mosquitoes were the disseminators of the yellow fever germ, it became urgent to show that these insects took into their tissues the organism, later supposed to be the cause of the disease. With this object in view, and believing erroneously as we know now, that the mosquito was in condition to transmit the infection as soon as it bit again, after becoming gorged with yellow fever blood, it was logical to suppose that the causative germ should be found in its proboscis immediately after feeding. In the numerous experiments carried out, not only the mosquito's sting and head were planted in various media, but it is described how some of the insects were seen to peck at the agar media and by the introduction of their proboscis, caused the subsequent development of tetracoccus colonies.

It is reported that only the particular tetracoccus resulted from these experiments and the natural deduction was

that, not only the means of transmission, but also the etiologic agent had been demonstrated. Unfortunately, neither the one nor the other could be corroborated at the time. Dr. Sternberg's Report, where he dismisses the question of Finlay's bacteria, says:

"There is no reason to believe that this organism has anything to do with the etiology of yellow fever and its occasional presence in blood drawn from the finger or in blister serum, is due to accidental contamination from the surface of the body or from the atmosphere."

A poignant lesson may be derived, however, from this series of experiments; it shows how even a master mind can go astray, not only when it deviates and plunges through the unexplored byways of new techniques, but specially when it is instigated by a desire, unwilling, yet evident, to fit the apparently indisputable facts, to preconceived ideas.

Please notice how men were working with avidity to solve the problem of yellow fever in the very foci of infection and mostly at about the same time; they were trying to take advantage of the methods that had been so successful in discovering the etiologic agents in tuberculosis, leprosy, anthrax, diphtheria, tetanus, typhoid fever, etc.

Probably the first investigator who abandoned the theory that the infection of yellow fever took place in the blood, was Dr. Paul Gibier, in Havana; he directed his researches to the alimentary tract. In this way, by emplaying the most scientific technique up to that time, he isolated a bacillus which was equally demonstrated by Sternberg to have been of no importance.

With the possible exception of Gibier, thus far, only men with little or no standing as bacteriologists had engaged in the fruitless search for the yellow fever germ; and their claims, as we have seen were quickly disposed of, but in 1897, a well-known investigator, Dr. Giovanni Sanarelli, who had obtained some renown by his work in the Pasteur Institute, particularly with typhoid fever, published a remarkable paper in the Annales of that institution, which on the most careful examination bore the imprint of truth. This report of the work carried out in Montevideo, Uruguay, was published in several languages, and in a comparatively short time the whole scientific world tacitly accepted Sanarelli's bacillus, (Bacillus icteroides,) and anxiously awaited the prophylactic serum which he announced as already undergoing manufacture.

Cultures of the B. icteroides were secured by various laboratories and experimental work begun for the purpose of verifying his findings; the results were most disappointing for the lack of uniformity.

Sanarelli did not fail to have staunch supporters for a while. De Lacerda and Ramos, in Brazil, though accepting the specificity of B. icteroides, endowed it with the most astounding pleomorphism. Dr. O. L. Pothier, though having found it only in three, out of fifty, yellow fever autopsies, at the Isolation Hospital in this city, (New Orleans,) concluded that "it is the special cause of yellow fever."

Drs. Wasdin and Geddings of the Marine Hospital Service, in a prelimi-

nary and separate report of work performed during the same epidemic, claimed to have found B. icteroides in thirteen out of sixteen cultures made from yellow fever cadavers, (the number not stated,) and Geddings declared that their "results indicate that the B. icteroides of Sanarelli is the specific agent in the causation of yellow fever."

In July, 1899, these gentlemen presented a complete and final report, the gist of which was that "in the blood of yellow fever cases extracted during life, Bacillus icteroides has been found in thirteen of the fourteen cases, with one negative, a percentage of 92.85."

Achinard and Woodson had also a leaning towards B. icteroides and claimed to have isolated it in 80% of cases in New Orleans.

More than ten other investigators in Brazil, Uruguay and Italy, by multiple experiments tried to demonstrate the validity of Sanarelli's contention.

It happened at the time that I was also engaged, under instructions from Surgeon General Sternberg, in the very same work as Wasdin and Geddings, in Havana. We frequently met at the autopsy table or in the hospital wards, so that the same cases served our purposes. I always made the autopsies and we all secured material and made plantings from the same cases. In due time, I rendered my report, (November, 1899,) including a period of six weeks spent at the yellow fever hospital in Santiago. My conclusions were as follows:

1. The specific organism in yellow fever is as yet an unknown entity in spite of the work reported by various observers; apparently new methods of cultivation must be introduced or new culture media devised in future research.

2. The B. icteroides of Sanarelli, lately asserted to be the causative agent of yellow fever is no more concerned in the production of this disease, than the common colon bacilli which are constantly found in the blood and viscera of individuals suffering or dead from yellow fever.

3. When approved bacteriologic methods are employed, the bacillus of Sanarelli does not as a rule appear in the cultures from the blood of yellow fever cases.

4. Bacillus icteroides may be and has been found present in the tissues of cadavers from other diseases.

5. The bacillus of Sanarelli when subjected to agglutination tests is not affected by the serum of yellow fever patients or convalescents.

In the meantime, Reed and Carroll, at the Army Medical School, had shown that B. icteroides belonged to the hog-cholera group of bacteria.

With all this evidence against it, B. icteroides would have been forgotten, after having entered all the contemporary text-books as the specific agent of yellow fever, had it not been that after the mosquito transmission of the disease had been demonstrated, some work was undertaken in this city, (New Orleans,) with the idea of bringing out whether the bacilli could not be passed around by the insects, through biting various animals.

Sanarelli in 1898 very quickly sold out his interest in the coming yellow fever prophylactic serum, in Montevideo, and sailed for home, far from the fields of investigation; he was

then appointed Professor of Hygiene in the University of Bologna, Italy, and subsequently became a Senator. As you know, from the viewpoint of science, he is quite dead.

I have gone a little more deeply into the Sanarelli boom of twenty-nine years ago, because I think a lesson can be derived from his activities and the stand taken by most honorable men in his support: it shows how a world-wide reputation, backed by enthusiastic though misguided investigators, can impose upon the scientific world a so-called parasite, to the extent of obtaining general acclaim and acceptance, overriding many apparently reasonable objections, requiring much time and painstaking labor on the part of others, before it could be knocked and definitely buried in oblivion.

In the field of yellow fever research, that work of demolition, so necessary at times, is much more difficult today than it was then, mainly for lack of material and the great expense entailed by the need of expeditions to distant lands.

However, as truth is bound to come out, resplendent, in the end, it is sure to do so now, as it did then.

Period from 1900 to date

From the facts noted heretofore we see, that with regard to the etiology of yellow fever nothing really had been accomplished up to the present century. Much had been done, however, in the study of the clinical and pathological aspects of the disease; the names of J. W. Ross, Stanford Chaillé, John Guitéras, Geo. M. Sternberg, Henry R. Carter and others, shall ever appear in the history of yellow fever as shining marks in their respective places.

After one year of military occupation of the Island of Cuba and the implantation of many sanitary improvements, it was found that the condition, as far as yellow fever was concerned, had not been materially affected; on the contrary, with the establishment of better and frequent communication with other towns, from Havana, epidemics broke out in new foci; a severe one developed in Santiago, (1899,) while the capital and its suburbs continued to be a source of worry to the sanitary authorities.

In May, 1900, the Surgeon General of the Army appointed a Board of medical officers, consisting of Maj. Walter Reed, as chairman, and Drs. James Carroll, Jesse W. Lazear and myself, officially to investigate the infectious diseases in the Island, but with instructions to devote special attention to the problems of yellow fever.

The Board convened on the 25th of June and learned of the direct and verbal instructions received by Maj. Reed from Gen. Sternberg. The work was distributed, by Reed assuming the direction, Carroll to do the bacteriologic and Lazear the pathological investigations, while I was to perform the autopsies and do the clinical work, having at the time charge of the Division Laboratory and a Ward for Tropical diseases at Military Hospital No. 1, in Havana.

During the month of July the work continued as above outlined in a more or less routine manner. An epidemic of yellow fever developed in

Santa Clara, a city in the center of the Island and eight hours from Havana by rail; several soldiers died from the disease and I was detailed to make such investigation as might trace the source of the epidemic and aid the medical authorities in establishing whatever preventive measures might seem proper. Capt. J. Hamilton Stone, in charge of the Military Hospital, had already done much of this and so upon this occasion and only incidentally, Capt. Stone and I spoke of the possible agency of insects in spreading the disease.

As to the actual cause of yellow fever we were still entirely at sea; it helped us little to know that a man could become infected in Havana, take the train for a town in the interior and start an outbreak there in the course of time.

In the early days of July, reports came from the troops stationed at the town of Pinar del Rio, in the western part of the Island, of a so-called epidemic of "pernicious malarial fever." I received orders to proceed there and report the actual condition of things. Upon the day of my arrival, July 19th, a soldier had just died of the fever; the autopsy revealed to me that he had died of yellow fever; a survey of the sick in camp and an examination of charts and records of previous cases, led me to report the existence of a severe epidemic and to initiate measures of isolation and the removal of the camp into the country. Major Reed joined me two days after and together we went over the records of the camp and hospital. Here we seemed to be in the presence of the same phenomenon remarked by Capt. Stone in reference to the cases at Santa Clara and before that, by several investigators of yellow fever epidemics; the infection at a distance, the apparently harmless quality of bedding and clothing of the sick. The possibility that some insect might be concerned in spreading the disease deeply impressed us and Maj. Reed mentions this circumstance in his later writings.

This was really the first time that the mosquito transmission theory was seriously considered by members of the Board and it was decided that, although discredited in spite of the repeated attempts of its most ardent supporter, Dr. Carlos J. Finlay, to demonstrate it, the matter should be taken up by the Board and thoroughly sifted.

On the first day of August the Board met and determined to investigate mosquitoes in connection with the spread of yellow fever. As Lazear was the only one of us who had had any experience with mosquito work, Maj. Reed thought proper that he should take charge of this part of the investigation in the beginning, while we, (Carroll and I,) continued with the other work at hand, at the same time that we became familiar with the manipulations necessary in dealing with the insects.

A visit was now paid to Dr. Finlay who, much elated at the news that the Board was about to investigate his pet theory, the transmission of yellow fever from man to man by mosquitoes, very kindly explained to us many points regarding the life of the one kind he thought most guilty and ended by furnishing us with a number of

eggs which, laid by a female mosquito nearly a month before, had remained unhatched on the inside of a half empty bowl of water in his library.

Much to our disappointment and regret, during the first week in August, Maj. Reed was recalled to Washington that he might, in collaboration with Drs. Vaughn and Shakespeare, complete the report on "Typhoid Fever in the Army." Thus we were deprived of his able counsel during the first part of the mosquito research. Maj. Reed was detained longer than he had expected and could not return to Cuba until early in October, several days after Lazear's death.

The mosquito eggs obtained from Dr. Finlay hatched out in due time; the insects sent to Dr. L. O. Howard, of Washington, for their classification were declared to be Culex fasciatus; later they have received various names and are now known as Aedes aegypti.

Lazear applied some of these mosquitoes to cases of yellow fever at "Las Animas" Hospital, keeping them in separate glass tubes properly labeled and everything connected with their bitings was carefully recorded; the original batch soon died and the work was carried on with subsequent generations from the same.

The lack of material at Quemados, near Havana, caused us to remove our field of action to the city, where cases of yellow fever continued to appear. We met almost every day at "Las Animas" Hospital, where Lazear was trying to infect his mosquitoes, or now and then I performed an autopsy and Carroll secured sufficient cultures to last him for several days of bacteriologic investigation.

Considering that, in case our surmise as to the insects' action should prove to be correct, it was dangerous to introduce infected mosquitoes amongst a population of 1,400 non-immune soldiers at Camp Columbia, Dr. Lazear thought best to keep his presumably infected insects in my laboratory at the Military Hospital No. 1, from where he carried them back and forth to the patients who were periodically bitten.

Incidentally, after the mosquitoes fed upon the yellow fever patients, they were applied, at intervals of two or three days, to whoever would consent to run the risk of contracting yellow fever in this way; needless to say, current opinion was against this probability and as time passed, and numerous individuals who had been bitten by insects that had previously fed upon yellow fever blood remained unaffected, I must confess that even the members of the Board who at first were rather sanguine in their expectations, became somewhat discouraged and their faith in success very much shaken.

Although the Board had thought proper to run the same risks, if any, as those who willingly and knowingly subjected themselves to the bites of the supposedly infected insects, opportunity did not offer itself readily, since Maj. Reed was away in Washington and Carroll, at Camp Columbia, engrossed in his bacteriologic investigations came to Havana only when an autopsy was on hand or a particularly interesting case came up for study. And so time passed and several Americans and Spaniards had subjected themselves in a sporting mood to be

bitten by the infected (?) mosquitoes without their suffering any untoward results, when Lazear applied to himself, (August 16th, 1900,) a mosquito which ten days before had fed upon a mild case of yellow fever in the fifth day of his disease; the fact that no infection resulted, for Lazear continued in excellent health for a space of time far beyond the usual period of incubation, served to discredit the mosquito theory in the opinion of the investigators to a degree almost beyond redemption.

This state of things, the gradual loss of faith in the danger which mosquitoes seemed to possess, led Dr. Lazear to relax a little and become less scrupulous in his care of the insects and often, applying them to patients, if pressed for time, he would take them away with him to his laboratory at Columbia Barracks, where, the season being then quite warm, they could be kept as comfortably as at the Military Hospital laboratory. Thus it happened that on the twenty-seventh of August he had spent the whole morning at "Las Animas" Hospital getting his mosquitoes to take yellow fever blood; this rather tedious work, on that day, lasted until nearly the noon hour, so that Lazear, instead of leaving the tubes at the Military Hospital, took them all with him to Camp Columbia; among them was one insect that for some reason or other had failed to take blood when offered it at the hospital.

This mosquito had been hatched at the laboratory and in due time fed upon yellow fever blood from a severe case, twelve days before, the patient then being in the second day of his illness; also at three other times, six days, four days and two days before. Of course, at the time, no particular attention had been drawn to this insect, except that it refused to suck blood when tempted that morning.

After luncheon that day, as Carroll and Lazear were in the laboratory attending to their respective work, the conversation turning upon the mosquitoes and their apparent harmlessness, Lazear remarked how one of them had failed to take blood, at which Carroll thought that he might try to feed it, as otherwise it was liable to die before the next day, (the insect seemed weak and tired); the tube was carefully held, first by Lazear and then by Carroll himself, for a considerable length of time, upon his forearm, before the mosquito decided to introduce its proboscis.

This insect was again fed from a yellow fever case at "Las Animas" Hospital on the twenty-ninth, two days later, Dr. Carroll being present though not feeling very well, as it was afterwards ascertained.

We three left the yellow fever hospital together that afternoon; on the following day, Lazear telephoned to me in the evening to say that Carroll was down with a chill after a sea bath taken a mile and a half from Camp and that they suspected he had malaria; we therefore made an appointment to examine his blood together the following morning.

When I reached Camp Columbia the mornig of August 31, I found that Carroll had already been examining his own blood, not finding any malarial parasites; he told me he thought he had "caught cold" at the beach; his suffused face, blood-shot eyes and gen-

eral appearance, in spite of his efforts at gaiety and unconcern, shocked me beyond words. The possibility of his having yellow fever did not occur to him just then; when it did, two days later, he declared he must have caught it at my autopsy room in the Military Hospital, or at "Las Animas" Hospital, where he had been two days before taking sick.

When we realized that Carroll had yellow fever, we searched in our minds for all possibilities that might throw the blame of his infection upon any other source than the mosquito that bit him four days before; Lazear, as he related to me the details of Carroll's mosquito experiment, in his desire to exculpate himself, repeatedly mentioned the fact that he himself had been bitten two days before, without any effect therefrom and finally what seemed to relieve his mind to some extent was the thought that Carroll offered himself to feed the mosquito and that he held the tube upon his own arm until the work was consummated. We there and then decided to test the same mosquito upon the first non-immune person who should offer himself to be bitten; this was of common occurrence and taken much as a joke among the soldiers about the military hospital. An hour had not transpired before we had obtained our purpose. As Lazear stood at the door of the laboratory trying to "coax" the mosquito from one tube into another, a soldier who was strolling by stopped to observe the performance; upon being asked, he declared that he did not believe in the possible risk of mosquito bites and offered himself almost spontaneously; as several mosquitoes took blood from his forearm, I noted on a slip of paper the necessary data:

William H. Dean, American by birth, belonging to Troop B, Seventh Cavalry; he said he had never been in the Tropics before and had not left the military reservation for nearly two months. The conditions for a test case were quite ideal.

Five days later, when he came down with yellow fever and the diagnosis of his case was confirmed by Dr. Roger P. Ames, U. S. Army, then on duty at the hospital, we sent a cablegram to Maj. Reed, still in Washington, apprising him of the fact that the theory of the transmission of yellow fever by mosquitoes, which at first was so much doubted and the transcendental importance of which we could then barely appreciate, had indeed been confirmed.

Both Carroll and Dean made an uninterrupted recovery; but we were to undergo the severest moral trial, compared to which the fearful days of Carroll's sickness dwindle into insignificance.

On the morning of the 18th of September, Lazear complained that he was "feeling out of sorts". I saw him the next day with all the signs of a severe attack of yellow fever. He assured us that he had not experimented upon himself, that is, that he had not been bitten by any of the purposely infected mosquitoes.

After the case of Dean so clearly demonstrated the certainty of mosquito transmission, we had agreed not to tempt fate by trying any more upon ourselves; we felt that we had been called upon to accomplish such work as did not justify taking risks which

then seemed really unnecessary. This we impressed upon Maj. Reed when he joined us in October, and for this reason he was never bitten by infected mosquitoes.

Lazear, during his illness told us, in his lucid moments, that five days before, at the yellow fever hospital, (Las Animas,) a mosquito had alighted on his hand and stung him, while he was engaged in feeding others from a patient; that it escaped before he could capture it, but that he entertained no fear from it, inasmuch as he had been bitten the month before and no infection had resulted therefrom.

Tuesday, the 25th of September, 1900, saw the end of a life that had been full of promise; one more name, that of Jesse W. Lazear, was graven upon the portals of immortality.

The state of mind in which this calamity left us cannot be adequately described. The arrival of Maj. Reed several days after in a great measure helped to relieve the tension of our nerves and render us a degree of moral support of which we were sorely in need.

We fully realized that three cases, two experimental and one accidental, were not sufficient proof, and that the medical world was sure to look with doubt upon any opinion based on such meager evidence; besides, in the case of Carroll, we had been unable to exclude the possibility of other means of infection, so that we really had but one indisputable case, Dean's, that we could present. In spite of this, we thought that the results warranted their presentation in the shape of a "Preliminary Note" and after the data were carefully collected from Lazear's records and those at the Military Hospital, a short paper was prepared which the Major had the privilege of reading at the meeting of the American Public Health Association, held on October 24th, in the city of Indianapolis.

For this purpose Maj. Reed went to the States two weeks after his return to Cuba and Carroll took a short vacation so as to fully recuperate, in preparation for the second series of inoculations which we had arranged to undertake, after the Indianapolis meeting, upon volunteers who, with full knowledge of the risks involved, would consent to suffer a period of previous quarantine.

Let us look for a moment into the origin of the mosquito theory.

The possible agency of insects in the propagation of yellow fever was thought of by more than one observer, from a very early period in the history of this disease. For instance, Rush, of Philadelphia, in 1797, noticed the excessive abundance of mosquitoes during that awful epidemic. Subsequently, several others spoke of the coincidence of gnats or mosquitoes and yellow fever but without ascribing any direct relation of the one regarding the other. Of course, man-to-man infection through the sole intervention of an insect was a thing entirely inconceivable and therefore unthought of until very recently, and in truth, the discovery, as far as yellow fever is concerned, was the result of a slow process of evolution of the fundamental fact, taken in connection with similar findings in other diseases.

The earliest direct reference is found in the writings of Dr. Nott, of Mobile, Ala., who in 1848 suggested

that the dissemination of the yellow fever poison was evidently by means of some insect "that remained very close to the ground". But the first who positively pointed to the mosquito as the spreader of yellow fever, who showed that absence of mosquitoes precluded the existence of the disease and who prescribed the ready means to stamp it out, by fumigation and by preventing the bites of the insects, was Dr. Louis D. Beauperthuy, a French physician, then located in Venezuela. I have an original copy of his paper, published in 1853, where he fastens the guilt upon the mosquitoes, believing, in accord with the prevailing teachings of the time, that they infected themselves by contact or feeding upon the organic matter found in the stagnant waters where they are hatched, afterwards inoculating the victims with their stings. He recognized the fact that yellow fever is not contagious and therefore could not think of the possibility of man-to-man infection, as we know it today. No one believed him, and the commission appointed to report upon his views said that they were inadmissible and all but declared him insane.

This field of investigation remained dormant for a comparatively long period of time. Meanwhile, another medical writer, Dr. Greenville Dowell, mentions in 1876, that "if we compare the effect of heat and cold on gnats and mosquitoes with yellow fever, it will be difficult to believe it is not of the same nature, as it is controlled by the same natural laws". Soon after this, in 1879, the first conclusive proof of the direct transmission of a disease from man to man was presented by the father of Tropical Medicine, Sir Patrick Manson, with regard to filaria, which the mosquito, as you know, takes from man and after a short time may pass it over to another subject. This discovery attracted world-wide attention and many looked again towards the innumerable species of biting insects that dwell in the Tropic Zone, as possible carriers of the obscure diseases which also prevail in those regions.

In 1881, Dr. Carlos J. Finlay, of Havana, in an exhaustive paper read before the Royal Academy of Sciences, gave as his opinion that yellow fever was spread by the bites of mosquitoes, "directly contaminated by stinging a yellow fever patient, (or perhaps by contact with or feeding from his discharges)". This view he held as late as 1900, which although correct in the main fact of the transmission of the germ from a patient to a susceptible person by the mosquito, the *modus operandi*, as he conceived it, was erroneous. Dr. Finlay, unfortunately, was unable to produce experimentally a single case of fever that could withstand the mildest criticism, so that at the time when the Army Board came to investigate the causes of yellow fever in Cuba, his theory, though practically the correct one, had been so much discredited, that the best known experts considered it as an ingenious but wholly fanciful one.

The important discoveries of Theobald Smith, as to the agency of ticks in spreading Texas fever of cattle, and those of Ross and the Italian investigators who showed conclusively that malaria was transmitted by a species of mosquito, brought the

knowledge of these various diseases to the point where the Army Board took up the investigation of yellow fever.

Perhaps I have gone too minutely into the manner in which the first series of mosquito infections took place under our hands and I hope it was not too wearisome to most of my hearers, but there were several points, not brought out in the strictly technical articles prepared at the time, which I thought should be put on record for the benefit of future historians.

The second and final series of experiments were made possible thanks to the public spirit and the moral support of Governor General Leonard Wood and by his appropriation of funds for the purpose.

An experimental camp was established and sufficiently safeguarded and there the men in small groups were brought in, kept under quarantine from eight to ten days, selecting only young healthy adults for the experiments, after they signed a document where they stated their willingness in spite of the possible risk incurred, always receiving an amount of money for their consent, with the three notable exceptions later explained.

In this, Camp Lazear, so named in honor to the memory of our departed colleague, besides the tents necessary for the men and guard, two small frame buildings, properly screened against mosquitoes, were erected.

Feeling that we had proved, to ourselves at least, the agency of the mosquito in yellow fever, it became our duty to disprove the theory, until then held as a certainty by many authorities, to the effect that the soiled bedding and clothing, the secretions and excreta of patients, were infectious and in some way carried the germ of the disease. We therefore utilized one of the small wooden buildings, with a capacity of 2,800 cubic feet. The walls and ceiling were absolutely tight, the windows and vestibuled door duly screened and all precautions taken to prevent the entrance of insects.

Into this room a stove, to maintain a high tropical temperature, was introduced; also three beds, mattresses and pillows, underwear, pajamas, towels, sheets, blankets, etc., soiled with blood and discharges from yellow fever cases; these articles were put on the beds, hung about the room and packed in a trunk and two boxes placed there for the purpose.

The building was finished and equipped on November 30th. That Friday evening, Dr. Robert P. Cook, U. S. Army, with two other American volunteers entered it and prepared to pass the night; they had instructions to unpack the boxes and the trunk, to handle and shake the clothing and in every way to attempt to disseminate the yellow fever virus, in case it were contained in the various pieces. We watched the proceedings from the outside, through one of the windows. The foul conditions which developed upon opening the trunk were of such a character that the three men were compelled to rush out of the building into the fresh air; yet, after a few minutes, with a courage and determination worthy only of such a cause, they went back and passed a more or less sleepless night, in the midst of an indescribably filthy environment.

For twenty consecutive nights these men went through the same performance; during the day they remained together, occupying a tent near their sleeping quarters. Dr. Cook, by voluntarily undergoing such a test, without any remuneration whatsoever, proved his faith in the mosquito theory; his demonstration of the harmless character of so-called infected clothing in yellow fever has been of the greatest importance.

A considerable number of enlisted men were anxious to submit themselves to the mosquito bites and thus aid in solving the mystery of yellow fever. Two particular cases require special mention. John R. Kissinger, a private in the Hospital Corps of the Army, was the first to offer himself, without any desire of pecuniary or other consideration and solely "in the interest of humanity and the cause of science"; the other, J. J. Moran, a civilian employe, also stipulated as a condition that he was to receive no pay for his services. Both these men, in due time, suffered from yellow fever and until very recently had never obtained any reward for the great risk which they ran so voluntarily and praiseworthily.

Kissinger became infected by having mosquitoes applied to him, while Moran obtained his yellow fever by lying down in the "infected mosquito building" and being bitten, of course, by several insects set free in the room for the purpose.

All the other cases in the persons of Spanish volunteers were produced by the bites of infected mosquitoes. After these experiments showed conclusively the transmission of the disease in this manner, it was produced also by the direct injection of yellow fever patients' blood subcutaneously, and later by blood serum that had been filtered through a Berkefeld bougie.

These experiments did not cause a single death.

The work of the Board showed,

1. That yellow fever is transmitted by the sting of mosquitoes now called Aedes aegypti;
2. That the mosquito becomes infected only when it stings the yellow fever patient during the first three days, possibly four days, of the disease;
3. That the mosquito becomes infective only after the 10th day, in Winter probably the 12th day, of taking the blood from the yellow fever patient;
4. That the period of incubation in man does not extend beyond six days;
5. That articles of clothing or excreta of yellow fever patients are not infective.

Since we made our demonstration in 1901, our work has been corroborated by various committees appointed for the purpose, in Cuba, Mexico and Brazil, composed variously of American, French, English, Cuban, Brazilian and German investigators. Nothing has been added to our original findings, nothing has been contradicted of what we have reported, and today, after twenty-seven years, the truths that we uncovered stand incontrovertible; besides they have been the means of stamping out yellow fever from

Cuba, the United States, (Laredo, Tex., 1903, and New Orleans, La., 1905,) British Honduras, Ecuador, Panama, Salvador, Colombia and most of Brazil.

The causative agent, the parasite of yellow fever, remains unknown in spite of the most commendable work later undertaken by Beyer, Pothier and Parker in Vera Cruz, (1902), Seidelin in Yucatan, (1911), and Noguchi in Ecuador, Mexico and Brazil, (1919 to date).

The *Leptospira icteroides* which, on epidemiologic grounds could not be accepted as the etiologic factor in yellow fever, has been identified as a twin brother of the leptospira of Weil's disease and shall soon, it is to be deplored, as occurred with Bacillus icteroides, disappear from further consideration in this connection.

Without the discovery of the germ, as is the case with rabies, yellow fever is now under control and I am confident that, for the good of mankind, it will finally be exterminated.

Havana, February, 1928.

REFERENCES

Achinard and Woodson: N. Y. Medical Journal, 1898.

Agramonte, A.: "Report on Bacteriological Investigations, etc." Medical News, February 10-17, 1900.

Bancroft, N.: "An Essay on the Disease called Yellow Fever, etc." London, 1811.

Beyer, Pothier and Parker: New Orleans Medical and Surgical Journal, 1902.

Boyce, R.: Transactions of the Society of Tropical Medicine and Hygiene, Vol. IV., pp. 33-130.

DeLacerda and Ramos: Archives de Médicine Expériment. May, 1899.

Finlay, C. J. and Delgado, C.: "Colonias de Tetrágenos Sembradas por Mosquitos," Academy of Sciences, etc. Havana, September 28th, 1887.

Finlay, C. J.: "El Mosquito Hipotéticamente considerado como Agente de Trasmision de la Fiebre Amarilla.' Anales dela Real academia de Ciencias, etc. Vol XVIII, p. 147.

La Roche, R.: "Treatise on Yellow Fever." Philadelphia, Pa., 1855.

Ligon, R.: "History of Barbadoes." London, 1697.

Noguchi, H.: Journal of Experimental Medicine, 1919, et seq.

Pothier, O. L.: Journ. of the Am. Med. Assoc., April 16, 1898, pp. 884-888.

Reed, W. and Carroll, J.: "B. Icteroides and B. Cholera Suis." Medical News, September 9th, 1899.

Reed, W., Carroll, J., Agramonte, A. and Lazear, J. W.: "The Etiology of Yellow Fever." A Preliminary Note. Trans. of the Am. Public Health Assoc. meeting, Oct. 24, 1900. (Indianapolis, Ind.)

Reed, W., Carroll, J. and Agramonte, A.: "The Etiology of Yellow Fever." An additional Note. Trans. of the Third Pan-American Medical Congress, Feb., 1901. (Havana, Cuba.)

Sanarelli, G.: "Etiologie de la Fievre Jaune." Annales de l'Institut Pasteur, 1897.

Seidelin, H.: Yellow Fever Bureau Bulletin. Liverpool, Eng., 1911-1912.

Sternberg, G. M.: "Report upon Preventive Inoculations in Yellow Fever." Washington, D. C., 1889.

Wasdin, E. and Geddings, H. D.: "Report of Commission, etc." Public Health Reports, 1898, Vol. XIII, No. 45.

Wasdin, E. and Geddings, H. D.: Medical News, August 26th, 1899, p. 266.

Metadysentery*

By Aldo Castellani, M.D., *Professor of Tropical Medicine, Tulane University of Louisiana, New Orleans*

Some years ago I introduced a new classification of bacterial dysenteries as follows:

1. *Bacterial dysentery, sensu stricto* (synonyms Shiga dysentery, Shiga-Kruse dysentery), due to dysentery organisms which do not ferment lactose or mannitol and do not clot milk (Shiga-Kruse bacillus).
2. *Paradysentery,* due to organisms which do not ferment lactose, ferment mannitol (acid only), do not clot milk (Flexner, Hiss--Russell, etc.).
3. *Metadysentery,* due to organisms, the metadysenteric bacilli, which, as is the case with the true dysentery bacilli, do not produce gas in any sugar, but either ferment lactose (acid only) and clot milk or ferment lactose (acid only) without clotting milk, or clot milk without fermenting lactose. (Organisms of the genus *Dysenteroides* and *Lankoides.*)

To make clear this grouping of bacterial dysenteries and dysentery bacilli, it is necessary to say a few words on the classification of the aerobic (facultative anaerobic) asporigenous, non-capsulated, gram-negative intestinal bacilli which do not liquefy gelatine or serum and do not produce pigment, viz., the tribe *Ebertheae* of Chalmers and myself; "Bacillaceae growing well on ordinary media, not forming endospores; aerobes and often facultative anaerobes; without fluorescence, pigment formation or gelatine liquefaction; without polar-staining, gram-negative, without a capsule."

The tribe Ebertheae may be subdivided into two subtribes:

(a) The organisms do not produce gas in glucose or any other sugar — Subtribe *Eberthoanaerogeneae.*

(b) The organisms produce gas in glucose and usually in other sugars — *Eberthoaerogeneae.*

The first subtribe contains six genera:

1. *Alkaligenes* Castellani and Chalmers.
2. *Vibriothrix* Castellani.
3. *Eberthus* Castellani and Chalmers.
4. *Shigella* Castellani and Chalmers.
5. *Lankoides* Castellani and Chalmers.

*Read before the American College of Physicians, Annual Clinical Week, Mar. 9, 1928, New Orleans, La.

6. *Dysenteroides* Castellani and Chalmers.

The second subtribe contains five genera:

1. *Salmonella* Lignières.
2. *Wesenbergus* Castellani and Chalmers.
3. *Enteroides* Castellani and Chalmers.
4. *Balkanella* Castellani and Chalmers.
5. *Escherichia* Castellani and Chalmers.

These eleven genera can be easily differentiated by using three media: milk, lactose, and glucose.

1. Genus *Alkaligenes*—Milk not clotted, (no change in the reaction of the medium, or alkaline); Lactose, no gas, (no change, or alkaline); Glucose, no gas (no change in the reaction of the medium, or alkaline).
2. Genus *Vibriothrix*—Same reactions as *Alkaligenes,* but the organisms of this genus are very polymorphic, vibrio-like, spirillum-like, bacillus-like; all the different forms may be found in the same preparation; they probably belong to the Higher Fungi (see Castellani and Chalmers' "Manual of Tropical Medicine," 3rd edition, p. 1068).
3. Genus *Eberthus*—Milk not clotted, Lactose no change, Glucose Acid, motility +.
4. Genus *Shigella*—Same characters as Eberthus but motility O.
5. Genus *Dysenteroides*—Milk not clotted, Lactose Acid, Glucose Acid.
6. Genus *Salmonella*—Milk not clotted. Lactose no change, Glucose Acid and Gas.
7. Genus *Wesenbergus*—Milk not clotted, Lactose Acid, Glucose Acid and Gas.
8. Genus *Enteroides*—Milk not clotted, Lactose Acid and Gas, Glucose Acid and Gas.
9. Genus *Lankoides*—Milk clotted (very slowly), Lactose no change or slowly acid, Glucose Acid.
10. Genus *Balkanella*—Milk clotted, Lactose Acid or no change, Glucose Acid and Gas.
11. Genus *Escherichia*—Milk clotted, Lactose Acid and Gas, Glucose Acid and Gas.

The differential biochemical characters of the above genera are summarized in Table I.

Classification of the Dysentery Bacilli.—The dysentery bacilli, according to the classification of Chalmers and myself, belong to the following three genera: *Shigella, Dysenteroides,* and *Lankoides,* of the tribe *Ebertheae,* subtribe *Eberthoanaerogeneae.* It may be of advantage perhaps to deal with these genera in a more detailed manner:

Genus *Shigella* Castellani and Chalmers, 1918.

Definition.—Ebertheae not fermenting lactose, glucose partially fermented with production of acid but no gas. Milk not clotted. Motility absent.

Type Species.—*S. dysenteriae* Shiga-Kruse, 1899.

Classification.—Several species have been described but the two generally admitted as valid are the following:

1. *S. dysenteriae* Shiga-Kruse.

2. *S. paradysenteriae* Collins.

The two species are differentiated by their behavior in mannitol: *S. dysenteriae* does not produce acidity, *S. paradysenteriae* produces acidity. Of *S. paradysenteriae* Collins there are several varieties, Var. *Flexneri*, Var. *Hissi-Russelli*, Var. *Strongi*, Var. *Duvali*, etc. The two best known are:

1. *S. paradysenteriae* Collins Var. *Flexneri* (so-called Flexner bacillus).

2. *S. paradysenteriae* Collins Var. *Hissi-Russelli* (so-called Y bacillus).

The two varieties are differentiated by their reactions in maltose; the Flexner variety produces acidity in maltose, the Hiss-Russell variety does not produce acidity in maltose. I have found that they differ also with regard to their reactions on starches; the Var. *Flexneri* produces acidity in potato and ginger, the Var. *Hissi-Russelli* does not touch those two starches.

Differentiation of S. dysenteriae Shiga-Kruse, S. paradysenteriae Collins Var. Flexneri, and S. paradysenteriae Collins Var. Hissi-Russelli by means of the Symbiotic Fermentation Phenomenon.—The symbiotic fermentation phenomenon has been described by me in previous publications. It may be defined as follows: "Two organisms neither of which alone produces gas in certain carbohydrates may do so when living in symbiosis or artificially mixed". For instance, *B. typhosus* alone does not produce gas in maltose (acid only), *B. Morgani* does not produce gas in that sugar (neither acid nor gas; the mixture *B. typhosus* + *B. morgani* produces gas. The phenomenon, as I have shown in other publications, may be of assistance in the classification of certain bacteria. The more important dysentery bacilli of the genus Shigella may be differentiated as follows: The symbiosis *B. dysenteriae Shiga-Kruse* *B. morgani* produces gas in maltose but not in mannitol; the symbiosis *B. paradysenteriae* Var. *Flexneri* + *B. Morgani* produces gas in maltose and mannitol; the symbiosis *B. paradysenteriae* Var. *Hissi-Russelli* + *B. Morgani* produces gas in mannitol but not in maltose.

TABLE III

Differentiation between *B. dysenteriae* Shiga-Kruse, *B. paradysenteriae* Collins Var. *Flexneri*, and *B. paradysenteriae* Collins Var. *Hissi-Russelli* by Their Fermentative Action on Mannitol and Maltose.

	Mannitol	Maltose	Remarks
Shiga-Kruse	O	AVS	Production of acid very slow
Flexner	A	A	
Y (Hiss-Russell)	A	O	

O = Absence of acidity and gas
A = acidity present
G = gas present
VS = Very slight

TABLE I

TRIBE EBERTHEAE

GENUS	LITMUS MILK	LACTOSE	GLUCOSE	REMARKS
Alkaligenes	O (Alk)	O (Alk)	O (Alk)	
Vibriothrix	O (Alk)	O (Alk)	O (Alk)	Same biochemical reactions as Alkaligenes but organisms are polymorphic, bacillus-like, vibrio-like and undulating filaments are often present in the same preparation. Probably belong to Higher Fungi (see Castellani and Chalmers' "Manual of Tropical Medicine," p. 1,068).
Eberthus	O	O	A	Motility present.
Shigella	O	O	A	Same biochemical reactions as Eberthus, but the organisms are non-motile.
Dysenteroides	O	A	A	
Salmonella	O	O	AG	
Wesenbergus	O	A	AG	
Enteroides	O	AG	AG	
Lankoides	C (slowly)	O or A	A	
Balkanella	C	O or A	AG	
Escherichia	C	AG	AG	

O = Negative, viz., absence of clotting in milk, absence of acidity and gas in sugar media
A = Acid
AG = Acid and gas
Alk. = Strongly alkaline
C = Milk clotted

Key for the Identification of the Genera of the Tribe Ebertheae

The following key may be found useful for the generic identification of intestinal organisms of the tribe *Ebertheae,* viz., non-capsulated; gram-negative, non-sporigenous bacilli which grow well on agar, are aerobic (faculative anaerobic), do not produce pigment, do not liquefy gelatine or serum.

TABLE II

Key to the Genera of the Tribe Ebertheae

So-called Alkaligenes, Typhoid-Dysentery, Paratyphoid, Coli Groups of Bacteria)

- **EBERTHEAE—GAS IN GLUCOSE** (Intestinal, non-capsulated bacili, which are aerobic [facultative anaerobic], grow well on agar, do not produce pigment, are non-sporigenous, non-bipolar staining, gram-negative, gelatine and serum not liquefied.)
  - Gas absent (O) **SUBTRIBE EBERTHOANAEROGENEAE—MILK**
    - Not clotted—Acidity in glucose
      - Absent (O or Alk)
        - bacillus, Alkaligenes
        - pleomorphic (bacillus, vibrio, spirillum) Vibriothrix
      - Present (A)—Lactose
        - O, motility
          - +, Eberthus
          - O, Shigella—Mannitol
            - O, Dysentery type *sensu stricto*
              - Shiga-Kruse
            - A, Paradysentery type—maltose
              - A, Flexner type
              - O, Y (Hiss-Russell type)
        - A, Dysenteroides
    - Clotted Lankoides
  - Gas present (+) **SUBTRIBE EBERTHOAEROGENEAE—MILK**
    - Not clotted—Lactose
      - O, Salmonella—Maltose
        - O, Morgan group
        - +, Saccharose
          - O, Paratyphosus group *sensu lato*
          - +, Asiaticus group
      - A, Wesenbergus
      - AG, Enteroides
    - Clotted—Lactose
      - A or O, Balkanella
      - AG, Escherichia—Saccharose
        - +, Section communior
        - O, Section communis

O = Negative result, viz., absence of clotting in milk, absence of acidity and gas in sugar media
+ = Positive, viz., presence of clotting in milk, presence of acid and gas in sugar media
A = Acid
G = Gas
AG = Acid and gas
Alk. = Strongly alkaline

The results of the symbiotic fermentation correspond to the results of the simple fermentation induced by the organisms themselves, viz., by symbiotic fermentation, gas is found in those carbohydrates in which the dysentery organisms alone produce simple acidity. The presence of gas, however, is much more striking in the case of Shiga-Kruse with regard to maltose—gas becomes evident much more rapidly than acidity to litmus. With regard to the symbiotic fermentation phenomenon, the reader may find all the details in papers published by me in the "Journal of the American Medical Association," Feb. 20, 1926, vol. lxxxvi, pp. 523-527, and in the Proceedings of the Society of Experimental Biology and Medicine, 1926, Vol LXXXIII, pp. 481-488, and 1927 (February).

TABLE IV

Differentiation between *B. dysenteriae* Shiga-Kruse, *B. paradysenteriae* Collins Var. *Flexneri*, and *B. paradysenteriae* Collins Var. *Hissi-Russelli* by Means of the Symbiotic Fermentation with *B. morgani*.

	Mannitol	Maltose
Symbiosis Shiga-Kruse + Morgani	O	G
Symbiosis Flexner + Morgani	G	G
Symbiosis Hiss-Russell + Morgani	G	O

O = absence of acidity and of gas; A = acidity present; G = gas present.

Genus *Lankoides* Castellani and Chalmers, 1918.

Definition.—The definition of this genus as given by Chalmers and myself ("Manual of Tropical Medicine", 3rd. edition, p. 938) is as follows: "Ebertheae fermenting glucose partially, with the production of acid, but no gas; lactose not fermented or only partially, without gas production. Milk clotted." It is important to note that the fermentation of lactose and the clotting of milk is often very slow.

Type Species.—Lankoides pyogenes (Passet, 1902).

Classification.—The principal species recognized as valid by Chalmers and myself are the following:

L. pyogenes (Passet, 1902).

L. ceylonensis "A" (Castellani, 1907).

L. ceylonensis "B" Castellani, 1907).

L. gintottensis (Castellani, 1910).

L. madampensis (Castellani, 1911).

Chalmers and I have given in our "Manual of Tropical Medicine" a key and a table for the recognition of these germs, based on certain biochemical reactions. This key and table, however, were based on the fermentation reactions shown by these germs after only a few days' incubation (3-6 days). I have found that if the organisms are incubated for a longer period, acidity appears in various sugars which at first are not touched; also certain strains, which, when recently isolated, apparently ferment only a very few sugars, later on after being subcultured several times, are

TABLE V

Genus Shigella

Castellani and Chalmers, 1918

(Reactions after an Incubation Period at 37° C. for 15 Days)

	Motility	Gram	Gelatine	Serum	Litmus Milk	Lactose	Glucose	Levulose	Maltose	Galactose	Mannitol	Dulcitol	Saccharose	Inulin	Isodulcitol	Inositol	Adonitol	Arabinose	Amygdalin	Salicin	Sorbitol	Raffinose	Dextrin	Erythrite	Glycerine	Ginger Starch	Potato Starch	Rice Starch	Indol	
S. dysenteriae Shiga-Kruse	O	O	O	O	O	O	A	A	O or A	A	O	O	O	O	O	O	O	O or A	O	O	O or A	O	O	O	O or A	O	O	O	O	Production of acid in maltose very slow
S. lunavensis Castellani 1912	O	O	O	O	As ALK	O	A	A	A	A	O	O	A	O	O	O	O	A	O	O	O	O	O or A	O	O or Avs	—			+	Differs from B. dysenteriae Shiga in fermenting saccharose and in producing indol
S. negombensis Castellani 1910	O	O	O	O	O or ALK	O	A	As	O	A	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	—			O	Not agglutinated by Shiga-Kruse serum
S. paradysenterica Castellani 1904	O	O	O	O	A	O	O or A	O	O	O or As	O	O	O	—	O	O	O	O	O	O	—	O	O	O	O	—			+ —	Not agglutinated by Shiga-Kruse serum
S. paradysenteriae Collins Var. Flexneri	O	O	O	O	O	O	A	A	A	A	A	O	O	O	O	O	O	A	O	O	O	O or A	O or A	O	O or Avs	A	A	A	+	
S. paradysenteriae Collins Va.r Hissi-Russelli.	O	O	O	O	O	O	A	A	O	A	A	O	O or A	O	O	O	O	A	O	O	O	O or A	O or A	O	O	O	O	O	+ —	
S. paradysenteriae Collins Var. Strongi	O	O	O	O	A ALK	O	A	A	O	A	A	A	A	O	A	—	O	A	O	O	A	A	O	O	O				+	
S. tangellensis Castellani 1911	O	O	O	O	As ALK	O	A	A	A	A	A	A	A	O	A	O	O	A	O	A	A	O or A	O or A	O	A	—	—	—	+	
S. metafaecaloides Castellani	O	O	O	O	ALK	O	A	A	A	A	A	O	O	O	—	—	O	O	O	O	A	A	A	O	—				O	

O = No change, viz., absence of clotting in milk, absence of acidity and gas in sugar media
+ = Positive, viz., presence of clotting in milk, presence of acid and gas in sugar media, etc.
A = Acid
ALK = Alkaine
As = Acid, slightly
Avs = Acid, very slightly
AG = Acid and gas

capable of fermenting many more sugars. For instance, most strains of *B. ceylonensis* A and *B. gintottensis* will give acidity in very many more sugars than those mentioned in our key and table if incubated for over a week; moreover, some strains serologically true may produce acidity in numerous carbohydrates even after a short incubation. The best way of differentiating the various species is therefore by serological methods. The study of their fermentative reactions (both simple and by using symbiotic fermentative reactions) may, however, be helpful in some cases.

From a practical point of view the organisms of the Lankoides group may be separated into two principal types:—

L. ceylonensis "B" type—indol positive, production of acidity in lactose usually fairly rapid.

L. ceylonensis "A" type—indol negative, production of acidity in lactose very slow, or absent. Clotting of milk may be extremely slow, taking 3 or 4 weeks.

Of each type there are several sub-types or varieties which are best differentiated serologically.

Inoculation in the lower animals.—Serological reactions.—Peptone water and broth culture of Lankoides ceylonensis "B" Strain RR., *Lankoides ceylonensis* "B", Strain RW, *Lankoides ceylonensis* "B", Strain O, inoculated subcutaneously (1 cc.-2 cc.) in rabbits, do not, as a rule, produce severe symptoms, although there are exceptions. Agglutinins are produced in a fair amount. The rabbits inoculated with any of the three strains of *L. ceylonensis* "B" will produce agglutinins for the homologous strain and for the other two strains of *L. ceylonensis* "B" in practically the same amount; as a rule, there is no agglutination for any strain of *L. ceylonensis* "A" or only slight; *L. ceylonensis* "A" serum does not agglutinate or only slightly strains of *L. ceylonensis* "B". *L. ceylonensis* "B" serum and *L. ceylonensis* "A" serum do not agglutinate *Lankoides madampensis.*

Genus Dysenteroides Castellani and Chalmers, 1918.

Definition.—Ebertheae fermenting lactose and glucose partially with the production of acid but no gas; milk not clotted.

Type Species.—Dysenteroides metadysentericus (Castellani, 1907). The first strain of this organism was isolated in 1904, but was not named for some years.

Remarks.—This genus contains several organisms, one motile (*D. bentotensis*) and several non-motile; *D. metadysentericus* "A", *D. metadysentericus* "B", *D. metadysentericus* "C", *D. metadysentericus* "D", which Chalmers and I differentiated by their sugar reactions. These varieties, however, are better separated by serological methods, as the sugar reactions have a rather marked tendency to vary. It must also be noted that a number of strains which at first appear as belonging to this genus, belong, in reality, to the Genus *Lankoides;* these strains, if kept in the incubator at 37° C. for less than two weeks will not clot milk, but if they are kept un-

TABLE VI
GENUS LANKOIDES

TABLE VI

Genus Lankoides

Castellani and Chalmers

(Reactions after an Incubation Period at 37° C. for Three Weeks)

	Motility	Gram	Gelatine	Serum	Litmus Milk	Lactose	Glucose	Levulose	Maltose	Galactose	Mannitol	Dulcitol	Saccharose	Inulin	Isodulcitol	Inositol	Adonitol	Arabinose	Amygdalin	Salicin	Sorbitol	Raffinose	Dextrin	Erythrite	Glycerine	Starch (Potato)	Indol	Lead Agar	REMARKS
L. ceylonensis "B" Castellani 1907 (Strain RR)	O	O	O	O	AC	A	A	A	A	A	A	A	O or A	O	A	O	O	A	O	O	A	A	A	O	A	O or A	+	O	
L. ceylonensis "B" Castellani 1907 (Strain RW)	O	O	O	O	AC	As	A	A	A	A	A	A	O or A	O	A	O	O	A	O	O	A	A	O	O	A	O or A	+	O	The four strains of *B. ceylonensis B* are serologically identical; strains RR and O produce acidity in lactose rapidly, strain RW very slowly.
L. ceylonensis "B" Castellani 1907 (Strain LV)	O	O	O	O	AC	A	A	A	A	A	A	A	A	O	A	O	O	A	O	O	A	A	A	O	A	A	+	O	
L. ceylonensis "B" Castellani 1907 (Strain O)	O	O	O	O	AC	A	A	A	A	A	A	A	O or A	O	A	O	O	A	O	O	A	A	A	O	A	A	+	O	
L. ceylonensis "A" Castellani 1907 (Strain PD)	O	O	O	O	AC	O or AVS	A	A	A	A	A	O	A	O	A	O	O	A	O	O	O	A	AS	O	A	O	C	D	
L. ceylonensis "A" Castellani 1907 (Strain O)	O	O	O	O	AC	O	A	A	A	A	O or A	O	O or A	O	O or A	O	O	A	O	O	O	A	AVS	O	O or A	O	O	—	Some strains of *B. ceylonensis A* at first produce acid in glucose only; lactose is not fermented, or only very slowly; milk is clotted very slowly.
L. ceylonensis "A" Castellani 1907 (Strain Z)	O	O	O	O	AC	A	A	A	A	A	A	O	A	O	A	O	O	A	O	O	O	A	O	O	A	O	O	O	
L. madampensis Castellani 1911 (Strain H)	O	O	O	O	AC	A	A	A	A	A	A	O	AS	O	A	O	O	A	O	O	AVS	A	A	O	A	O	+	O	
L. pyogenes foetidus Passet 1902	+	O	O	O	AC	A	A	A	A	A	A	A	A	—	—	—	—	A	—	—	—	A	A	—	—	—	+	—	

O = Negative, viz., absence of clotting in milk, absence of acidity and gas in sugar media (medium may become alkaline)
+ = Positive, viz., presence of clotting in milk, presence of acidity and gas in sugar media, etc.
A = Acid
C = Milk clotted
AS = Acid, slightly
AVS = Acid, very slightly

der observation for more than two or three weeks their reactions are those of the genus *Lankoides,* milk becoming clotted.

Animal Experiments.—Toxic Action on Rabbits.—When broth or peptone water cultures are injected in ordinary doses (½ to 1 cc.) most strains are not toxic. Olivi, with a strain of *B. metadysentericus,* induced the death of a rabbit 5 days after a single injection of a 3 cc. dose, while rabbits inoculated with 2 or 1 cc. did not die. In the rabbits that died, the post-mortem showed inflammatory lesions similar to those found in rabbits inoculated with Shiga-Kruse.

Remarks on the Bacilli of the Genus Lankoides and of the Genus Dysenteroides (Metadysentery Bacilli)

In practice it is useful to combine the two genera *Lankoides* and *Dysenteroides* into one group: the *Lankoides--Dysenteroides* group, or *Dysenteroides sensu lato,* or "metadysentery bacilli", because certain organisms which at first present the characters of the genus *Dysenteroides* after a prolonged incubation may show the characters of the genus *Lankoides,* viz., they will clot milk.

The "metadysentery bacilli" (*Lankoides-Dysenteroides* group) are similar to the dysentery bacilli *sensu stricto* (genus *Shigella,* "dysentery-paradysentery" bacilli) in that they do not produce gas in any sugar; they differ from them, however, as they either produce acidity in lactose and clot milk, or produce acidity in lactose without clotting milk, or they clot milk without producing distinct acidity in lactose. Some of these bacilli have been known for years; *Bacillus ceylonensis* "A" and "B" were found by me in 1904 and 1905, their full description being published in 1907; and I isolated a strain as long ago as 1901, although it was not classified at the time—it is still in my collection. *B. gintottensis* I described in 1910; *B. madampensis* I isolated in 1910 and described in 1911; the first strain of *B. metadysentericus* was isolated in 1904, but was not named for some years. Chalmers and I created for these organisms two genera: *Lankoides* and *Dysenteroides.* Nabarro has given much attention to this group of organisms; he is inclined to identify them all with *B. coli anaerogenes* of Lembke, and in a very interesting publication in the "Journal of Pathology and Bacteriology," 1923, vol, xxvi, pages 429-430, states the following:

> "Lemke in 1896 isolated from the excreta of dogs a coliform bacillus producing acid but not gas in glucose and lactose media, to which he gave the name *B. coli anaerogenes.* Between 1905 and 1912 Castellani isolated several varieties in Ceylon which he has named *B. ceylonensis, B. madampensis, B. bentotensis.* These organisms all agree in the property of fermenting sugars, etc., with the formation of acid alone, the difference between them being of a minor nature."

Nabarro further states that he first isolated *B. coli anaerogenes* in 1912 from a case of dysentery at the Wakefield Asylum. In 1921 during an in-

TABLE VII

Genus Dysenteroides

	Motility	Gram	Gelatine	Serum	Litmus Milk	Lactose	Glucose	Levulose	Maltose	Galactose	Mannitol	Dulcitol	Saccharose	Inulin	Isodulcitol	Inositol	Adonitol	Arabinose	Amygdalin	Salicin	Sorbitol	Raffinose	Dextrin	Erythrite	Glycerine	Potato Starch	Indol
D. metadysentericus Castellani Var. "A"	O	O	O	O	A	A	A	A	A	AS	A ⊙ or O	O or AS	A	O	—	—	—	—	—	—	—	—	—	—	—	—	+ O +
D. metadysentericus Castellani Var. "A" (Strain Z)	O	O	O	O	A	A	A	A	A	A	A O	O O	A O	O	A O	O	O	A	O	O	O	A	O	O	O	O	O
D. metadysentericus Castellani Var. "B" (Strain L)	O	O	O	O	A	A	A	A	A	A	AS or O	AS or O	AS or O	O	A or	O	O	A	O	O	A	A	A	O	A	—	+
D. metadysentericus Castellani Var. "C"	O	O	O	O	A ALK D	AS	A	A	AS	A	AVS	AVS	AVS	—	—	—	—	—	—	—	—	—	—	—	—	—	O
D. metadysentericus Castellani Var. "D"	O	O	O	O	ALK A or	AS	A	A	A	A	A	A O or	A	—	—	—	—	—	—	O or	—	O or	—	—	—	—	+
D. bentotensis Castellani	+	O	O	O	A,ALK	A	A	A	A	A	O	AS	A	O	O	A	O	O	O	AS	O	AS	O	O	A	—	+

O = Negative, viz., absence of clotting in milk, absence of acidity and gas in sugar media (the medium may become alkaline)
+ = Positive, viz., presence of clotting in milk, presence of acid and gas in sugar media, etc.
A = Acid
AB = Acid and gas
ALK = Alkaline
— = Reaction unknown
AS = Acid, slightly
AVS = Acid, very slightly
D = Decolorized

vestigation upon summer diarrhea and other diarrheal conditions in children, he isolated 30 strains of *B. coli anaerogenes* from 25 patients out of 107 investigated.

There is much to be said in favor of Nabarro's theory that the anaerogenes bacilli isolated by me and later by himself, Sonne and others are identical with *B. coli anaerogenes* of Lemke. As, however, since 1905, I have always found constant serological differences between the principal organisms of the group, I have retained in this paper in its general lines the classification introduced by Chalmers and myself.

Clinical Syndromes Associated with the Presence of the Metadysentery Bacilli

The clinical intestinal conditions in which organisms of the metadysentery bacilli have been isolated and for which the term "metadysentery" *sensu lato* (a term introduced by me some years ago) might be applied, may be classified as follows:

(a) *Acute.*—With either dysenteric diarrhea or simple diarrhea.

(b) *Chronic.*—Several types.

These organisms have also been found at times in obscure cases of fever in which intestinal symptoms may be very slight or lacking altogether.

Chronic Colitis associated with Organisms of the Metadysentery Group.—(Synonyms: Chronic lankoides-dysenteroides colitis; chronic dysenteroides colitis; chronic metadysenteric colitis, chronic metadysentery).

In this paper I wish to discuss a chronic type characterized by recurrent attacks of simple diarrhea with absence or only occasional presence of dysenteric symptoms. The stools during the attack are fluid, brownish or yellow, at times frothy; as a rule they do not contain muco-pus or blood, but there are a number of exceptions. Each attack may begin suddenly with severe abdominal pain, or only abdominal discomfort may be felt; it lasts from a few hours to several days. In the intervals between the attacks, and the intervals may be very prolonged, the patient may feel fairly well, but as a rule complains at times of slight abdominal discomfort and flatulency; he often feels run down, tired, nervous and not inclined for work. These cases go on for years, a little better, a little worse; they consult many practitioners, and are generally told they are suffering from "colitis or ""intestinal intoxication" or "intestinal subinfection"; sometimes the diagnosis "mucous colitis" and "abdominal neurasthenia" is made. Not rarely atypical appendicitis is suspected and the patient is operated on. The patients try all sorts of treatment, Plombières douching being probably the most popular and next to it streptococcal vaccines and various so-called intestinal disinfectants. The result is generally unsatisfactory. Some of these patients have a wretched life and are a burden to themselves and their families.

Diagnosis.—This is difficult; the bacteriological examination of the stools may be negative very many times before metadysentery organisms are found. In the chronic cases what

I have found most helpful is testing the blood for agglutination for the principal varieties of the group. My routine procedure is to test the blood of every suspicious case for agglutination first of all for *B.ceylonensis B.* B. *ceylonensis A,* and *B. metadysentericus* Z. When the agglutination is higher than 1 in 80, as a rule repeated bacteriological examinations of the stools will reveal sooner or later the presence of metadysentery organisms, although, as I have already stated, many examinations may have to be carried out before a successful one is obtained.

Differential Diagnosis.—A very similar chronic clinical syndrome may be found caused by *E. histolytica;;* also, though very rarely, by bacilli of the true dysenteric group (Shiga-Kruse and Flexner). Only repeated and thorough microscopical and bacteriological examinations will enable one to make a differential diagnosis.

Illustrative Cases (recent cases).—Case I: Mrs. V. for the last two years has been suffering at intervals from attacks of diarrhea with severe abdominal pains, the stools being brownish or yellowish, at times somewhat frothy, never containing any blood. She came to consult me in June this year. A bacillus was isolated from the stools, with the characters of the bacilli of the genus *Lankoides,* viz., produced no gas in any sugar, produced acidity in lactose, clotted milk, slowly. The blood agglutinated the bacillus isolated from the stool up to a dilution of 1 in 160, and the laboratory strain of *B. ceylonensis* B up to a dilution of 1 in 120. The bacillus was not agglutinated by blood of normal individuals. A powerful Shiga serum (titre for Shiga), 1: 1,000, obtained from Burroughs-Wellcome, agglutinated it only up to 1 in 20. The lady was admitted to a tropical nursing home and was kept at complete rest in bed and on fluid diet. She had at first a dose of castor oil, and then bismuth and salol. A course of *Lankoides* vaccine (peptone water cultures killed by the addition of carbolic ½ per cent.) was given in minute doses. She gradually got better, and up to the present day has not had any attacks. The agglutination for the bacillus isolated from the stools rapidly decreased; it is now negative.

Case II.—Mrs. D., Englishwoman, had an acute attack of diarrhea with probably a little blood and mucus, 12 years ago in Rome. She did not go to see a doctor, and did not even go to bed; since then she has never been quite well. Very often she had abdominal discomfort and flatulency; as a rule, however, no diarrhea. She came to consult me in August, 1926, because she was passing through a period of reactivation with diarrhea, the stools being liquid of brownish colour.

A bacillus was isolated from the stool with all the characteristics of the *Lankoides* group, viz., slow clotting of milk, no production of gas in any sugar, acidity in glucose. I thought at first that lactose was negative, but after three weeks a slight amount of acid developed. Serologically the organism was identical with a strain of *B. ceyloncnsis* A isolated in Ceylon. The bacillus isolated from the stool was agglutinated by the patient's blood in a very high dilution of 1 in 3220; the laboratory strain of *B. ceylonensis* A was agglutinated in a dilution of 1 in 160.

*Case III...*Mr. H. K. for the last two years has been suffering from attacks of diarrhea, with abdominal discomfort; apparently there was never any blood or muco-pus in the stools. He came to consult me in July of last year after a more than usually severe attack; he was still having three to six motions a day, which were liquid, somewhat frothy, and of a brownish colour. The examination of a stool passed by the patient in a sterile vessel in the laboratory showed absence of blood and pus; no amebae or flagellates present; no eggs of worms. A bacteriological exam-

ination was carried out in the usual way. On MacConkey's plates several white colonies appeared in addition to numerous red colonies. Some of the white colonies were further investigated, and a bacillus with all the characteristics of the one found in Case II was found (*B. ceylonensis* A.) *This* bacillus was also serologically identical with the bacillus isolated in Case II. The patient refused to enter a nursing home owing to pressure of business; he was put on a strict diet; he took regularly some so-called intestinal disinfectants, and had a course of injections of vaccine prepared from his own bacillus. To date he has had no further attacks. The patient's blood agglutinated equally well (1:160) the bacillus isolated from the stool and the bacillus isolated from Case II. The agglutination limit for the laboratory strain of *Lankoides ceylonensis* A was 1:80.

Case IV.—Mrs. H. has been suffering from rather obscure abdominal symptoms for many years; abdominal discomfort, flatulency, attacks of simple diarrhea with long periods of constipation; there was apparently at time slight tenderness in the right lower abdomen; appendicitis was suspected and an operation was performed. The appendix did not seem to be diseased. The lady came to consult me in August, 1926, merely complaining of vague abdominal discomfort and of always feeling tired and ill. The blood showed high agglutination (more than 1:160) both for *Lankoides ceylonensis* A and for *Lankoides ceylonensis* B, all strains; none for *Lankoides madampensis.*

Bacteriological Investigation of Stools.—Three strains of *Lankoides* were isolated, one was agglutinated by the patient's blood and by *Lankoides ceylonensis* B serum; the third strain was not agglutinated by either the patient's serum or *Lankoides ceylonensis* A or *Lankoides ceylonensis* B sera. The third organism appeared to be identical with *Lankoides madampensis.* It would seem therefore, that in this case the condition was probably due to a mixed infection—*Lankoides ceylonensis* B + *Lankoides ceylonensis* A.

Case V.—Miss V., Australian, for the last ten years has been suffering from vague abdominal discomfort with occasional attacks of diarrhea; the stools never contained blood, according to her statements. She is somewhat nervous and anemic. The physical examination of the abdomen does not reveal anything abnormal. The bacterial examination of the stool shows presence of metadysentery bacilli, of the type *B. ceylonensis* A. The strain isolated from the stools is agglutinated by the patient's blood in a dilution of 1 in 320; the laboratory strains of *B. ceylonensis* A in a dilution of 1 in 80; the laboratory strain of *B. ceylonensis* B, 1 in 40; the laboratory strain of B. *dysenteriae,* Shiga-Kruse, is not agglutinated; the laboratory strain of *B. dysenteriae,* Flexner and Hiss-Russell, are agglutinated in a dilution of 1 in 10.

Old Cases.—I may quote two cases given in a publication of mine in the *Journal of Hygiene* (vol. vii, No. 1, January, 1907.)

(1). An Australian medical man, 24 years of age, arrived at Colombo from China in April, 1905. A week before reaching Colombo he began to feel ill with lassitude, headaches, diarrhea—10 to 15 motions daily with no mucus or blood—irregular low fever. The disease lasted two months. The diarrhea was followed by a long period of constipation. The convalescence was very prolonged, the patient suffering repeatedly from attacks of nervous tachycardia. A bacillus was isolated which clotted milk and produced acidity but no gas in many sugars; I gave a description of the bacillus and called it *B. ceylonensis* B. The original strain is still in my possession.

(2). A retired German officer. Strongly-built man, 50 years of age. No previous disease of any kind. Began to feel ill with malaise while on board a German steamer during the voyage from Aden to Colombo: irregular rises of temperature; slight diarrhea. He never felt ill enough to remain in his cabin. As there was a

case of enteric on board, the same disease was suspected in this patient, and he was accordingly advised to land at Colombo. During the first three days after landing in Colombo he felt quite well and was getting ready to go up country when suddenly, in the afternoon, his temperature rose to 103.2°. There was slight shivering, severe headache, *diarrhea becoming a prominent symptom*, twelve liquid motions being passed in a few hours. I saw the patient in the evening: temperature 102.4°, pulse 78; no roseola or any other rash; examination of the chest negative; spleen not enlarged; the stools, which were liquid and yellowish, did not contain blood or muco-pus. The fever lasted sixteen days longer and its course was very irregular. The pulse always remained slow. The spleen could never be palpated, and roseolar spots never appeared. The diarrhea lasted for three days, and the stools never contained blood.

The analysis of the urine was negative. Except during the first four days, the patient did not complain of headache or of any serious subjective symptom.

Treatment consisted in the exhibition of the usual intestinal antiseptics and in keeping the patient on liquid diet. From the stools an organism was isolated which clotted milk, slowly produced acidity in glucose, but not in lactose (reading taken on the seventh day). I called the bacillus *B. ceylonensis* A. It is interesting to note that the bacillus became capable later on of producing acidity in a number of sugars, and occasionally it may produce slight acidity in lactose after two to three weeks' incubation.

Conclusions

(1) There are several clinical condition in which organisms of the *metadysentery group* (*Lankoides-Dysenteroides* group) have been found. These conditions may be acute, subacute, or chronic. There may be dysenteric diarrhea or there may be simple diarrhea. In certain cases fever may be present and may be a prominent symptom, so much so, that some form of enteric or parenteric may be suspected.

In this paper I have called attention to a chronic type of colitis characterized by recurrent attacks of diarrhea, generally simple diarrhea, but occasionally dysenteric for brief periods of time. Between the attacks the symptoms are somewhat indefinite and obscure. The patient feels tired, disinclined for work, nervous, and often complains of slight abdominal discomfort and flatulency. The symptoms are so indefinite that very different diagnoses are made: intestinal intoxication, intestinal subinfection, mucous colitis, abdominal neurasthenia; not rarely atypical appendicitis is suspected and an operation is performed.

(2) The metadysentery bacilli are intestinal bacilli similar to the dysentery bacilli, Shiga and Flexner, with regard to certain characters, viz., they do not produce gas in any sugar; they differ, however, from them as they either clot milk and produce acidity in lactose, or they clot milk without producing distinct acidity in lactose, or they produce acidity in lactose without clotting milk. Some species of the so-called metadysentery bacilli group (*Lankoides-Dysenteroides* group) are pathogenic, others probably are not. The two principal species I found in 1905 and published in 1907 and 1908, viz., *B. ceylonensis* B and *B. ceylonensis* A are, in all probability, pathogenic, and so is the *Bacillus metadysentericus* described by me. In the chronic conditions I have discussed, the blood of the patient generally contains a large amount of agglutinins for the variety of metadysentery bacillus isolated from the patient's stools, as

well as the same variety isolated from other patients with the same symptoms. In one of the recent cases (Case IV) three varieties of *Lankoides* were isolated from the stools—two (*B. ceylonensis* B and *B. ceylonensis* A) were agglutinated equally well by the patient's blood, and the agglutinins were specific; the third variety, a strain of *B. madampensis*, was not agglutinated, and was probably non-pathogenic. This case was probably one of mixed infection caused by a strain of *B. ceylonensis* B + *B. ceylonensis* A of the metadysentery group.

I shall be pleased to supply workers interested in the subject with cultures of *B. ceylonensis* B, *B. ceylonensis* A, and certain strains of *B. metadysentericus*.

My thanks are due to Sir William Simpson for having carried out the animal inoculations in England.

LITERATURE

(1) Bhattacharyya, 1926: Brief Note on the Morphology, Cultural Characters and Biochemical Reactions of Vibriothrix zeylanica Castellani. Journ. Trop. Med and Hyg., Nov. 15.

(2) Castellani, 1907: Cases of Fever Confounded with Typhoid. Journ. of Hyg., vol. vii, No. 1, Jan.

(3) Ibid, 1911: Reports of the Advisory Committee for the Tropical Diseases Research Fund.

(4) Ibid, 1912: Observations on some Intestinal Bacteria found in Man. Centralblatt f. Bakteriologie, 65 Band, Heft 4-5.

(5) Ibid, 1916: Infezioni tifiche, paratifiche e miste della zona Adriatico-Balcanica. Annali di Medicina Navale e Coloniale, 1916, Fasc. v-vi.

(6) Ibid, 1918: Alcune osservazioni sulla etiologia, diagnosi e cura della dissenteria. Annali di Medicina Navale e Coloniale, anno xxiv, vol. 1, fasc. 1.

(7) Ibid, 1918-1919: Reports of the Inter-Allied Sanitary Commission, Office International d'Hygiène Publique.

(8) Castellani and Chalmers, 1919: Manual of Tropical Medicine, Chapters on Classification of Bacteria.

(9) Castellani, 1920: Classification de certain groupes de bacilles aerobies de l'intestin humain. Annales de l'Institut Pasteur.

(10) Castellani, 1927: The Classification of Bacterial Dysenteries and of Dysentery Bacilli. Amer. Journ. Trop. Med., July.

(11) Castellani, 1927: Observations on a little-known Group of Anaerogenic Intestinal Bacteria. Proc. Roy. Soc. Med., vol. xx.

(12) Castellani, 1927: Further Observations on the Action of Bacilli of the Paratyphoid Dysentery and Metadysentery Groups on Various Starches. Journ. Trop. Med. and Hyg., Sept. 15.

(13) Castellani, 1927: Further Observations on the Symbiotic Fermentation Phenomenon. Journ. Trop. Med. and Hyg., Oct. 1.

(14) Nabarro, 1923: Journ. Pathology and Bacteriology, vol. xxvi.

(15) Olivi, 1923: The Virulence of Bacillus metadysentericus (Castellani) in the Rabbit. Its Resistance to the Action of Sunlight. Journ. Trop. Med. and Hyg., April 16.

(16) Peruzzi, 1926: Morphological and Cultural Investigation of Vibriothrix zeylanica, Castellani. Journ. Trop. Med. and Hyg., Feb. 1.

(17) White, P. Bruce, 1926: Further Studies of the Salmonella Group. Medical Research Council, His Majesty's Stationery Office, Special Report Series, No. 103.

(18) Castellani, 1927: Notes on the Etiology of Certain Cases of Recurrent Diarrhea and Certain Obscure Forms of Colitis Due to Bacteria of the Metadysentery Group. Journ. of Trop. Med. and Hyg., Nov. 15, 1927.

Some Observations of Intestinal Amebiasis Due to Infection with Entamoeba Histolytica*

By Wm. M. James, M.D., F.A.C.P., *Consultant in Tropical Medicine for the United Fruit Company, Panama Canal Zone*

THAT manifestation of intestinal ulceration due to infection with *E. histolytica* and known as amebic dysentery has been fully described with reference to its etiology, pathology, symptomatology and diagnosis. The dysentery itself may be due to a generalized ulceration of the entire large bowel with consequent colitis, or the ulcers may be confined to the sigmoid and rectum, and dysentery may follow this localized irritation.

For some years past it has also been known that quite severe and extensive amebic ulceration of the cecum, or the flexures, or other individual parts of the large bowel may occur without dysentery, or the lesions may be only a few ulcers, localized or distributed. In such cases there may be occasionally a bloody stool, but more often diarrhea alternating with constipation, and the symptomatology is varied in the extreme, so much so that the diagnosis cannot be made except by the finding of the specific agent, *E. histolytica.*

The many phases of the life cycle of this parasite will later be referred to briefly.

*Read before the American College of Physicians, New Orleans, Clinical Week, March 9, 1928.

I will say at present only that in the small precystic and cyst-forming stages *E. histolytica* is difficult to find, and in fresh preparations from the stools, may easily be confused with similar phases of *E. coli, Endo. nana,* and *Iodamoeba butschlii,* all three of which are frequently seen in the examination of the stools, and especially in sub-tropical and tropical countries. Nearly twenty years of work on this subject has convinced me, and, I may add, others better qualified than myself, that the correct diagnosis in fresh material of intestinal amebiasis not associated with dysentery, and the proper identification of the four species of amebae commonly found in the stools, is a task requiring long and special training, and is not to be entrusted, as it so often is, to the ordinary worker in the laboratory or the inexperienced technician.

The milder cases of intestinal amebiasis rarely come to autopsy except when complications such as liver abscess or perforation occur, or when death results from accident or some intercurrent disease or infection. Although the association between amebic abscess of the liver and dysentery has been notorious for many years; and indeed autopsy records show that

when death follows untreated generalized intestinal ulceration due to *histolytica* infection there is abscess of the liver in over 50% of such cases, there are many reports of abscess of the liver on record without history of dysentery, and at autopsy the pathologist finds only a few scattered lesions, perhaps in the cecum, perhaps elsewhere in the large bowel.

These are cases of amebiasis without dysentery, and the lesions, when uncomplicated by dysentery, may persist for years with few and intermittent symptoms. The pathologist, however, as far as I have been able to ascertain, has until very recently confined his researches to the gross and microscopic study of the larger lesions themselves and it has not occurred to him that there may exist quite extensive damage to the mucous membrane of the large intestine that is not readily visible macroscopically, or at least only after very careful inspection. Such a condition has been suspected by several workers, particularly, Dobell, Boeck, Wenyon and Craig, and although it has been found as a very early condition in the cat, it has only recently been demonstrated in man. I shall endeavour briefly to indicate the importance of this conception of amebiasis without dysentery.

In the stools of many apparently healthy and normal persons, sometimes with a history of previous dysentery or diarrhea, less frequently in those who have never had intestinal troubles, enormous numbers of the small *vegetative, precystic* and *cystic* forms of histolytica are found, quite as numerous as the larger vegetative forms found in acute dysentery. And it is not at all unusual to find the parasite persisting in quantity under these conditions. It is well known that these very small forms measuring from six to ten micra are derived from the large vegetative forms living higher in the bowel, and represent that phase of the life cycle preparatory to encystment.

Now, some authorities, among them those above mentioned, have held that *histolytica* is always a true parasite of the human tissues, and that it must invade these in order to live. But if the enormous number of the small generations found at times in the stools of apparently normal persons actually represent tissue invasion higher in the bowel, such invasion would certainly result in severe ulceration with corresponding symptoms, and this does not inevitably occur. To explain this discrepancy it has been suggested that the invasion is confined only to the mucosa, and that the lesions heal readily, so that a continuous process of invasion and healing with complete restoration of the mucous membrane is taking place. These authorities do not agree that the parasite can live normally in the lumen of the bowel, and invade the tissue only at intervals, a hypothesis that would correspond to observed facts. They also maintain that the large number of active vegetative forms found in acute dysentery do not live and multiply in the lumen of the bowel, but generate in the tissues, and are thrown into the lumen by ruptures of the abscesses and discharges from the ulcers in the wall of the large intestine.

On the other hand there are those, among whom at present I am found, who hold that *histolytica* can live normally in the lumen of the upper part of the large bowel, and invades the tissues only under certain conditions, such as those which tend to irritate the mucosa, or when resistance is lowered.

We base our opinion on the grounds that the number of parasites frequently encountered, in mild amebiasis as well as in acute dysentery, is out of all proportion to that found in sections of the intestinal wall in either case. Also, the well known tendency of a mild *amebiasis* to pass quickly into acute dysentery following dietary indiscretions or lowered resistance due to intercurrent disease, is evidence that something besides a latent tissue invasion has awakened a dormant infection into activity. It is only very recently, as I shall explain later, that proof has been obtained to show that large sections of the wall of the large intestine can be invaded without macroscopic lesions, and here no evidence of healing has been found, but rather a progressive damage.

Whichever hypothesis may be correct, there is one certain fact common to both, and concerning which practically all authorities are in agreement, and that is, whether it is always a tissue parasite, or whether it can live harmlessly for long intervals in the lumen of the bowel, *histolytica* is invariably an enemy of its host, actively or potentially, and should be treated as such whenever and wherever found.

Another important and frequently overlooked factor in *histolytica* infection is the relative immunity of the human host. It is indeed fortunate that this is true, otherwise the ulceration would go on to perforation, and most of these infections would be followed shortly by a fatal peritonitis. The muscle layers of the large bowel offer a very considerable resistance to the passage of the amebae. One sees frequently large ulcers with few or not any amebae at the edges, and in many instances the damage is out of all proportion to the number of amebae present. So true is this that many believe a secondary bacterial infection from the lumen of the bowel is as responsible as the *amebae* themselves, and frequently there is no correlation between the number of *amebae* present and the amount of the damage, especially in *amebic* abscesses of the liver, lung, brain and spleen.

This fact may offer a clue to the successful treatment of *amebic* infection. If the lesions in the wall of the large bowel can be made to heal perhaps the *amebae* in the tissues will die, and this can be demonstrated in pathological sections. Nests of *amebae* in the tissues of the large intestine are invariably associated with abscess or ulcer formation communicating with the lumen of the bowel, although these nests may lie outside of the actual ulcerative process itself.

Conversely it may be said that if the amebae in the lumen of the bowel are removed, and re-infection prevented, the tissues will take care of their own amebae.

The usual description of an amebic ulcer is that it is flask or crater-shaped, pointing into the lumen of the

bowel, with its edges undermining the mucosa, and at times penetrating the muscle coats and even the serosa. According to Dr. H. C. Clark, when the external muscle coat has been for the most part destroyed, the intestinal bacteria can pass through the serosa, and bring about a localized or general peritonitis. This process is often accompanied by a considerable hypertrophy of the wall, especially of the submucosa, and if the ulcer is advanced, by the formation of adhesions and bands.

The amebae are said to gain entrance through the crypts of Lieberkühn, from the bases of which they wander into the submucosa, and pass out radially in that tissue, the end result being the flask-shaped or crater ulcer just described.

This description is essentially correct as far as it goes, but it is not sufficiently inclusive. The amebae not only penetrate the lumina of the the gland cells and the basement membrane, but not infrequently there is a direct invasion of the interstitial tissue as well. The result of this is a lysis and destruction of the mucosa, sometimes over large areas, without typical ulcer formation and without much invasion and destruction of the sub-mucosa. Dr. Lawrence Getz, pathologist to the Santo Tomas Hospital in Panama, has demonstrated this process over six inches or more of the mucosa, unaccompanied by ulcer formation or destruction of the sub-mucosa. He has also found the very earliest type of lesion, so rarely that it might be thought merely a post-mortem change, were it not for the amebae found in the tissues.

Again, there may be an almost complete destruction of the mucosa, over large spaces, without ulceration and with very little invasion of the submucosa. Such damage cannot fail to give rise to symptoms, and it is pathology of this type, with a few ulcers here and there, that is responsible for the clinical manifestations of amebiasis without dysentery.

Notwithstanding the careful studies of recent years, the exact mechanism by which *histolytica* produces tissue destruction is still undetermined. The earliest form of damage is very similar to that produced by chemical agents, a true lysis of the cells, without a reaction accompanied by round cell and *leukocytic* infiltration, a phenomenon that occurs later, and it may be due partly to bacterial invasion. But in all probability the amebae secrete a ferment that has a true *lytic* action against the tissue cells, and this is especially true in the so-called sterile abscesses of the liver and brain, where there is great tissue destruction without scondary bacterial invasion. But even in very early lesions without secondary bacterial infection and round cell infiltration, the damage is often out of proportion to the number of amebae present, and if the *lytic* action of the ferment be so powerful here, one might look to see this action continued later. It does not appear that gland cells are more susceptible than interstitial tissue, since in the latter, and especially between the glands themselves, areas of necrosis with few amebae are constantly found.

Very early there is also a marked congestion and at times a thrombosis of the terminal vessels of the circulatory

system, especially of the *capillaries* and the very small radicles of the *venous portal system.* This has been explained by stating that in the crater- or flask-shaped ulcers there is a stasis of the blood supply due to pressure and round cell infiltration.

But this congestion accompanies the very earliest lesions also, long before any mechanical factor can possibly be concerned, or any reaction due to secondary bacterial infection has taken place. It is a striking and constant phenomenon and suggests that even prior to invasion of the tissue by the amebae, these have brought about some irritation at the surface of the mucosa which results in this reaction. In its turn this brings up the thought that it is possible for *histolytica* to remain latent in large numbers in the lumen of the bowel, but when the occasion arises, for reasons as yet unknown to us, they begin to secrete a ferment irritative to the mucosa, and armed with this weapon of offense, hitherto unused, they begin their invasion.

I offer this suggestion solely for what it is worth. In truth there is so much about the mechanism of *histolytica* infection which is at present hidden from us, and it is so difficult to reconcile or to correlate the known facts and recent findings with any hypothesis, that I feel sure we must work for a long time yet, before we can postulate a definite and satisfactory conclusion.

It is not possible within the limits of this paper to discuss all the factors in amebiasis. If we have a definite knowledge of the essential facts of the pathology it is possible to induce from these most of the symptomatology. I shall merely state that this is variable in the extreme. Intestinal amebiasis can simulate, directly or reflexly, practically every known gastro-intestinal disease, from simple indigestion, with flatulence and occasional colic, to obstruction and cancer. I have several times seen amebic infiltration of the cecum and transverse colon mistaken for cancer, and with very good reason. Amebic typhilitis and non-amebic chronic appendicitis resemble each other so closely that the diagnosis often cannot be made until operation, and even here the two will frequently be associated.

With respect to diagnosis, it is my own opinion that except in cases of acute or subacute dysentery where the large, active, vegetative form is readily demonstrated, the findings in the fresh stools should be checked with permanent preparations. This is because in other types of amebiasis *histolytica* appears in the stools for the most part in the small vegetative or precystic stage, and here, in fresh preparations, it is very easily confused with *nana, butschlii,* and even with *coli.* It is true that a qualified expert working with absolutely fresh material, may be able to distinguish between these four species in the examination of fresh material. But such experts are few and far between, and are not often found in the practice of medicine or in attached laboratories.

Dobell well intimates that if the diagnosis cannot be made correctly, it should not be made at all, and since the treatment at best is tedious for patient as well as physician, a correct determination is of highest import-

ance. This determination can be made with a very high degree of probability in the wet fixed or permanent preparations, by anyone capable of reliable clinical laboratory work. In fresh material it cannot be made at all except by those with long and special training, and thoroughly familiar with the elements of microscopy. Yet in more than one medical center untrained technicians are finding histolytica in a high percentage of fresh stool examinations, and clinicians are attributing a vast variety of *infirmities* from Hodgins' disease to chronic arthritis, to infestation with this parasite.

Some of such errors in diagnosis, which I have encountered recently, I would not have believed possible, had I not seen them myself, to borrow a term of that eminent authority Prof. Clifford Dobell.

Treatment of Endamebiasis*

By Philip W. Brown, M.D., *Division of Medicine, The Mayo Clinic, Rochester, Minnesota*

THE introduction of ipecac and its derivations of various emetin compounds was thought to be the solution of a difficult therapeutic problem. With the passage of time ipecac and emetin have proved to be efficient in controlling the symptoms of acute amebiasis but they have proved a disappointment in a large group of cases with regard to eradicating the parasite. In the last few years it has been realized that treatment must be carried out along broader lines, and hence, many new preparations have been added.

Willner has recently reviewed his results with the use of yatren, stovarsol and auremetin. His cases were traced for from three to six months after treatment and from three to six stool examinations were made. The results were good in 90 per cent of eighty-eight cases in which yatren was used, in 90 per cent of thirty-seven cases in which stovarsol was used, and in 92 per cent of forty cases in which stovarsol and auremetin were used. Auremetin is the hydrogen periodide of emetin in combination with the dye auramine, a drug introduced by Martindale and first used clinically by his associate, Willmore. The drug contains 28 per cent emetin and is administered in four one-grain doses by mouth on alternate days for a week. On the intervening days stovarsol is given. I have used auremetin in too few cases to evaluate it. Nausea and usually vomiting have been produced by the doses recommended so far and I have had to decrease it to 2 grains daily. Emetin is of immense value. It has been shown that if it is used alone a large percentage of cases relapse (1, 17) but the combination of an organic arsenical compound and emetin seems to be the best therapeutic measure. If auremetin should prove to be as useful as now seems probable, the hypodermic syringe may be dispensed with and all medication given by mouth, except in acute cases in which emetin administered hypodermically will still remain the most effective means of controlling the disease rapidly.

In an endeavor to evaluate the therapeutic results of some of these drugs the work during the last three years in the Mayo Clinic has been reviewed. Sixty-three cases of an earlier report (2) on the use of stovarsol are

*Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine, 1928.

included, as additional data on many of these have been obtained.

It is impossible to trace all patients treated in the clinic. Many patients begin treatment and continue under the supervision of their home physicians. Less than half of the patients treated here have been observed long enough to be included in this report. This study, therefore, is based on the data obtained from a group of 178 cases from which enough data are available to give some idea of the therapeutic efficiency of the treatment employed.

As a basis for efficiency of treatment the eradication of the parasite is held paramount. It is important to remember that the patient is more concerned with the subjective results than with the laboratory observation; in nearly all cases in which ameba is a cause of the trouble the patients respond promptly to treatment and most of them are soon restored to a state of normal efficiency. I have found that when *Endamoeba histolytica* is present and is a factor in the complaint, treatment of even a few days will prove this association of organism and complaints and yet the treatment may seem to have eradicated the parasite while the symptoms persist. This applies particularly to carriers, and thus any statements as to benefiting various ailments by treating the ameba must be guarded. Treatment is indicated from the public health standpoint and to protect the carrier from possible diarrhea following an acute illness, operation or from an abscess of the liver. If the attacks of diarrhea are steady or intermittent, the prospects of relieving the condition are more definite. Here, again, there are exceptions to the rule, such as the possible influence of achlorhydria, or indeterminate diarrhea which bears some resemblance to sprue or pellagra.

It is not my intention to discuss incidence or diagnosis, but I shall again call attention to the value of making stool examinations for three successive days at least. In 112 cases (63 per cent) the ameba was identified in the first stool; in forty-four (24 per cent) it was identified in the second stool and in eighteen (10 per cent) in the third. Hence in 97.7 per cent of this series the ameba was recognized by three examinations. The remaining cases were identified by making smears from rectal ulcerations or from the pus of a draining abscess of the liver.

Types of Treatment

Stovarsol (acetylaminohydroxyphenylarsenic acid) was first used in the treatment of endamebiasis by Marchoux in 1924. Since his first favorable report its use has extended to all countries. The original suggestion of giving the drug in 0.75 gm. doses daily for a week has been changed to the same dosage daily for four or five days. Intolerance to the drug has been reported frequently; the milder reactions of toxic erythema did not cause undue concern but a number of cases of exfoliative dermatitis occurred. Two deaths have been reported (11, 19).

When the drug was first used in the Mayo Clinic (March 1925) the dosage was 0.75 gm. daily for seven days but was gradually reduced until

it was given for four days. The immediate as well as the later results seemed to be as effective with the shorter course. If there was no intolerance, two or three more courses were given with an interval of ten days between courses.

In discussing results the expression "seem to be cured" will be used; the word cure demands prolonged observation and repeated stool examinations which is possible in few instances. When the term, seem to be cured, is used it will imply a disappearance of symptoms and at least two or more negative stool examinations.

Of the 178 patients treated, 130 received stovarsol only; five received both emetin and stovarsol. Of the 135 patients, 109 (80 per cent) seemed to be cured, of the twenty-six patients who had recurrence twenty-four took stovarsol again without benefit and two seemed to be cured by additional stovarsol. In the group of twenty-four treparsol (formyl amide of meta-amino-para-oxyphenyl-arsenic acid) appeared to effect the cure of three and not of four; yatren (iodo-oxybenzenpyridin - sulphonate) appeared to effect the cure of four and not of five; six patients were only temporarily benefited from bismuth emetin iodide and emetin. In the group of recurrences the patient with abscess of the liver, who died, is included.

Treparsol (formyl amide of meta-amino-para-oxyphenyl-arsenic acid) was first suggested in the treatment of amebiasis by Flandin in 1924, but its use has not been extensive. Treparsol was used first in the clinic in February 1926. My attention was directed to it by the statement that it was eliminated more rapidly than stovarsol. Stovarsol was effective but it was desirable to minimize all risks incident to its use. The apparently slow elimination might be a factor in reactions or in the development of neuritis. In order to ascertain the degree of absorption and ratio of elimination of arsenic in the urine and feces, following treparsol by mouth, an investigation was undertaken in collaboration with Osterberg. This work is being continued; from the data already available certain facts seem to be established.

Six patients (Table 1) received a course of treparsol treatment which consisted of 0.75 gm. daily for four days. This amount of treparsol con-

TABLE I

SUMMARY OF RESULTS FROM ARSENIC

ARSENIC ELIMINATED MG.			RATIO OF ARSENIC IN URINE TO ARSENIC IN THE FECES	COMMENT
URINE	FECES	TOTAL		
192	595	787	1:3	Treparsol chewed
184	546	730	1:3	Treparsol chewed
133	815	948	1:6	Treparsol chewed
45	741	786	1:16	Treparsol swallowed
70	645	715	1:9	Treparsol swallowed
125	1005	1130	1:8	Treparsol swallowed

tains approximately 800 mg. of arsenic. The daily collection of urine and feces was begun at the onset of the treatment and continued for seven days. The arsenic estimations were made after the electrolytic Gutzeit method, as described by Osterberg. Prior to the adoption of this method the estimations had been made in five cases according to the ordinary Gutzeit method in which there is a preliminary oxidation of organic matter by alkaline fusion or by potassium chlorate. A quantitative recovery of arsenic in biologic materials was not obtained by this method.

The results of the estimations by the electrolytic method show that the major portion of the arsenic is eliminated in the feces. When the treparsol tablets were swallowed, the ratio of arsenic in the urine to that in the feces varied from 1:8 to 1:16. If the tablets were chewed thoroughly, the dispersion of the arsenic was greater and the ratio of arsenic in the urine to that in the feces was 1:3 or 1:6.

The manner in which the drug becomes effective is not known. Reports summarized by Stokes indicate that the ratio of elimination of arsenic in urine and feces is comparable to the results with treparsol in the Mayo Clinic. He further showed that the chief storage depots for arsenic are in the liver, spleen, and intestinal tract. The amount of arsenic in the walls of the intestine is evenly distributed according to the experimental work of Clausen and Jeans. It is not known whether or not there is constant absorption of arsenic by the entire intestine but it would seem that the effectiveness of treparsol may depend more on the amount of arsenic in the wall of the bowel than on the amount in the content of the bowel. The disease process in endamebiasis is in the wall of the bowel and it would appear desirable to use a drug which obtains access to the walls of the colon either by direct absorption or by virtue of its presence there as a result of arsenic in the blood stream. It would seem that the ameba would be more affected by the drug in the mucosa and submucosa than by its direct action as it passes along in the fecal current. There must be an individual variation in the absorption of arsenic as is shown by the two cases in which only 45 mg. and 70 mg. were excreted in the urine. It is possible that one of the explanations for the reaction of the skin to the drug may be found in the fact that certain persons may absorb the drug more rapidly or eliminate it more slowly than in the cases in which there is no difficulty. Opportunity has not been afforded to study this question since in the cases in which elimination studies were made the patient did not suffer from reaction.

In each of the six cases studied, approximately all of the arsenic was eliminated by the end of the seventh day after treatment was begun. The variations in the total output of arsenic, compared to the intake of approximately 800 mg., merely illustrate the almost unavoidable discrepancy in biologic materials. Particles of the tablet may or may not be included in an estimation of the drug in feces and this will cause an apparent discrepancy. The estimation of

the drug in the urine should be accurate although there is the possibility that one or more specimens may be lost during the week. The results are sufficiently accurate to warrant the conclusion that approximately all of the arsenic is eliminated three days after the completion of a course of twelve tablets and if four or five additional days are permitted to elapse before the institution of a second course, the chances of an accumulative effect are slight. Treparsol was given in 0.75 gm. doses for five days and shortly decreased to four days because of experience gained in its use. Thirty-nine patients were first treated with treparsol, thirty-eight of whom seemed to be cured. Eleven of these were given 4 to 14 grains of emetin in addition to the treparsol and none had a recurrence. Seven patients who had had stovarsol were given treparsol and three of these seemed to be cured. Hence forty-six patients received treparsol either at the onset of treatment or following recurrence after the use of stovarsol. Of these forty-six patients five (11 per cent) had recurrences and forty-one (89 per cent) seemed to be cured. This is comparable to the 80 per cent result with stovarsol as the treparsol series is smaller and the drug has not been used as long as stovarsol. Reactions have occurred, similar to those with stovarsol. One death from its use has been reported.

Only a few patients who suffered from recurrence following stovarsol or treparsol received more than temporary benefit by continuing the drug. There is some risk in persevering with either arsenic or emetin indefinitely and it is advisable to change to other drugs or different combinations. Certain patients who have been treated with only one or two drugs have continued to suffer from diarrhea. Changing drugs has been successful in several instances.

The group of twenty cases (Table 2) shows what may be accomplished by changing to a different drug or to a combination of drugs. Although these patients may not be actually cured, the results have been encouraging, particularly as all patients had had more or less persistent treatment which was of only temporary benefit. In one case the patient had been treated intensively with arsphenamine, emetin, bismuth emetin iodide and so forth, but diarrhea persisted. In fact the disease had persisted long enough (twenty years) to produce contracture of the rectum, a complication that may develop in chronic cases, and emphasized the foothold the ameba had gained. The patient was given 20 gm. of treparsol in divided courses; a year later diarrhea had stopped and examination of four stools was negative. Three months later he returned to have an operation for anal fistula; there was no recurrence.

The intestinal tract as a depot for arsenic may be an explanation for failure to obtain permanent benefit from the use of stovarsol or treparsol. Strains of ameba may become tolerant to the prolonged presence of the arsenic in the wall of the intestine. This theory has been suggested by various syphilographers in the case of resistant syphilis when it is thought that certain strains of the *Treponema pallidum* may become tolerant to the drug.

TABLE II

VALUE OF VARYING TREATMENT IN RECURRENT CASES

CASE	DURATION OF DIARRHEA, YEARS	FORMER TREATMENT	PRESENT TREATMENT	COMMENT
22	1.5	Stovarsol	Yatren and stovarsol	Seemed cured; four negative stools
23	1.5	Stovarsol and emetin course	Yatren	Seemed cured; four negative stools
26	30	Stovarsol and three courses emetin	Treparsol, emetin and yatren	Seemed cured; reported five months later no diarrhea
30	4	Emetin course, bismuth, emetin iodide	Treparsol	Seemed cured; three negative stools; reported well three months later
31	20	Emetin, arsphenamine, ipecac, bismuth and bismuth emetin iodide	Treparsol	Seemed cured; six negative stools one year later; four negative stools and no diarrhea
39	5	Emetin	Stovarsol	Seemed cured; two stools negative six months later
52	0.16	Stovarsol	Yatren	Seemed cured; three stools negative three months later; reported well eight months later
64	1	Emetin course	Stovarsol	Seemed cured; one stool negative one year later
70	25	Emetin	Treparsol	Seemed cured; two negative stools
76	9	Emetin and Stovarsol	Yatren	Seemed cured; three negative stools; reported well two months later
90	1	Stovarsol, treparsol, emetin and yatren	Treparsol and Emetin	Seemed cured; three negative stools
92	6	Emetin course	Treparsol and Emetin	Seemed cured; four negative stools
94	13	Emetin course	Stovarsol	Seemed cured; three negative stools; four months later reported no more diarrhea
98	4	Emetin course	Stovarsol	Seemed cured; three negative stools

TABLE II (Continued)

VALUE OF VARYING TREAT MENT IN RECURRENT CASES

CASE	DURATION OF DIARRHEA, YEARS	FORMER TREATMENT	PRESENT TREATMENT	COMMENT
111	10	Emetin course	Treparsol and yatren	Seemed cured; three negative stools; one year later three negative stools and no diarrhea
148	0.5	Treparsol	Yatren	Seemed cured; three negative stools; six month later reported no diarrhea
154	1.3	Stovarsol	Yatren	Seemed cured; three negative stools; three months later reported no diarrhea
155	1	Emetin	Yatren	Seemed cured; three negative stools; four months later two negative stools and no diarrhea
158	4	Emetin and stovarsol	Yatren	Seemed cured; two negative stools; three months later no diarrhea
160	10	Emetin	Treparsol	Seemed cured; three negative stools

Another possibility is suggested by the observation that certain persons may take stovarsol for long periods without apparent injury, and thus may merely keep the activity of the ameba at a point to enable them to continue work. There seems to be a state of "armed neutrality" whereby the parasite and the host continue to progress the former in spite of the arsenic and the latter in spite of the ameba as long as arsenic is taken. Two patients have consumed what would seem to be an enormous amount of arsenic and yet have not been relieved, nor has any demonstrable injury from the arsenic resulted. In one of these the patient has recently received yatren and seems to be cured. The other patient has tried emetin, yatren, and the arsenical compounds but is still distressed; in order to continue work he resorts to frequent courses of stovarsol. One is inclined to speculate on the possibility of injury later, particularly the change that may ultimately take place in the liver. The same may be true of emetin. It has seemed to me that emetin-fast strains of ameba develop in certain persistent cases of diarrhea (1). Dale and Dobell have suggested that the actual amount of emetin in the blood stream is much less than the amount required to destroy the ameba experimentally. From this they consider that there may be a change in the reaction of the host as a result of prolonged administration of emetin and that this, rather than a change of

ameba to an emetin-fast organism, is the explanation.

From a practical standpoint, the present conclusion is that variation in treatment in recurrent cases is indicated. Ipecac, various emetin compounds, and organic arsenical compounds for both oral and intravenous administration and iodine in the form of yatren are available as remedies. Other remedies, although less effective as a rule, are Chapparo amargoso, massive doses of bismuth subnitrate, irrigations of the colon with hot (42 to 44°C) solution of sodium chloride, kerosene, and so forth.

Because of increasing experience with treparsol and stovarsol and a certain number of recurrences it was thought that a combination of treparsol or stovarsol and emetin might prove more effective than either drug used alone. This regimen was carried out in eighteen cases. One of hepatic abscess need not be considered in evaluating the remainder of the group. This patient was practically moribund before treatment was instituted. In the remaining seventeen cases there are two known recurrences, and six patients who were well from three to twelve months after completing treatment. At present, treatment is begun with both emetin and treparsol unless the patient has previously been given either or both of the drugs. In such instances yatren is employed at the beginning of treatment.

Iodo-oxybenzenpyridin - sulphonate (anayodin, yatren) was first used in the treatment of amebiasis by Menk in 1922. Its use spread first to the Orient and Far East; few reports are available of its efficiency in this country. Turner and Jones reported a group of eight cases in which yatren was used. Willner reported favorable results in seventy-nine of eighty-eight cases in China. In a review of the literature he found that from 66 to 92 per cent of patients were believed to be cured by yatren. It is given by mouth in 3 gm. doses daily for a week and repeated after a week's interval for two or more such doses. Oral administration in conjunction with irrigations of the colon of 1 to 2 per cent yatren is recommended by many. The drug may increase the diarrhea so that the amount of the drug given daily must be decreased. Other untoward symptoms from its use have not been observed. Irrigation has not been used in The Mayo Clinic. Yatren was first used in April 1926 and has been given to eighteen patients in this series. Eleven of these seemed to be benefited while seven suffered further recurrences, the latter had had emetin, treparsol or stovarsol and usually bismuth emetin iodide. The same gamut of treatment was run by seven patients treated successfully. It is possible that better results might have been obtained by irrigations of yatren in conjunction with the oral administration.

The results in this small group indicate that yatren is valuable in the treatment. If it were used first, the percentage of favorable results might be as high as with arsenic, as Willner's article seems to indicate. For the present yatren is administered to patients who have had recurrences either in the clinic or elsewhere after taking arsenic or emetin. Emetin and

arsenic have failed in such cases and yatren is used for two main reasons: first, to give either the host or the parasite a change from previous treatment, and second, to minimize the possibility of the accumulation of arsenic or emetin.

Additional Data on the Results of Treatment

Data from reëxamination of patients after a period of three months are shown in Table 3. Fifty-eight of the patients seemed to be cured from three to many months after completion of treatment. If more than six months had elapsed without symptoms and the stools were negative, and if amebic dysentery again appeared, the possibility of reinfection is as strong as that of recurrence. It is better, however, to consider such conditions as recurrences for it is difficult to prove reinfection. The majority of the twenty-seven patients known to have recurrence were observed to have symptoms soon after cessation of treatment. There were a few exceptions and again there is the temptation to seek the explanation by reinfection rather than by recurrence.

In two instances the date of recurrence was not recorded. The case of abscess of the liver need not be considered in estimating the time of recurrence. Of the remaining twenty-four cases there was recurrence in eighteen, or almost 75 per cent, within eight weeks, in three cases there was recurrence within four months, and in two cases within six and eight months respectively.

MacAdam found that thirteen of eighteen relapses occurred within four weeks and Gordon that 65 per cent appeared within two months.

Table III

Cases in Which Cure Had Apparently Been Effected

Time After Treatment, Months	Two to Ten Stools Negative; Clinically Well	Stools Not Examined; Clinically Well	Total
3	11	7	18
6	19	5	24
12	9	2	11
12+	4	1	5

Hence there are available subsequent data concerning fifty-eight patients apparently cured and concerning twenty-seven with recurrence. Some of the remaining ninety-three patients may have had recurrences but one derives consolation from the fact that failures are usually reported.

Complications of Treatment

Stovarsol or treparsol was used in 174 cases. In six (4.4 per cent) of 136 cases in which stovarsol was given, toxic erythema developed from the fifth to the tenth day. The dosages ranged from 3.75 to 5.25 gm. In three (6.5 per cent) of forty-six cases in which from 3 to 9 gm. of

treparsol had been given, toxic erythema developed. In two cases it appeared on the fourth and fifth day, while in one it did not occur until after the completion of the second course of the drug. In one case in which enough of a skin reaction developed to be considered a mild manifestation of exfoliative dermatitis, treparsol was used.

In some of the cases in which erythema developed an antecedent acute upper respiratory infection was thought to have some possible relationship to the development of the skin reaction. Morgan suggested that arsenic may produce enough irritation of the mucous membranes to simulate coryza. In either event, it is safer to withhold arsenic temporarily if the patient has a cold or tonsillitis. Also, if the slightest suspicion of skin irritability develops, or if any peculiar symptoms are mentioned by the patient, it is well to withhold the drug until all doubt is gone.

In the nine cases of toxic erythema, recovery was complete within a week. The patients were kept in bed as long as fever persisted. Fluids were increased and a moderate amount of alkalies given by mouth. Three patients received, intravenously, sodium thiosulphate; while this probably increased the rate of elimination of arsenic, it did not exert any outward effect on the dermatitis or shorten the illness. The patients were advised against the further use of arsenic but were told to rely on an emetin preparation, yatren, bismuth, and so forth. The advice was disregarded by one patient who took both emetin and stovarsol later. Mild peripheral neuritis developed although a skin reaction was not reported. In two other cases in which stovarsol was given peripheral neuritis developed. In one case 7.5 gm. of stovarsol had been given in divided courses while in the other several courses with a total of at least 22.5 gm. of the drug given. In both cases arsenic was present in the urine many weeks after stovarsol had been taken. The slow elimination of the arsenic should explain the neuritis and emphasize caution in the amount and repetition of courses of the drug. Individual susceptibility is significant in these complications as in all types of drug reaction. Jaundice as a complication in the use of stovarsol or treparsol has not occurred in any of my cases.

Results of Treatment in Various Types of Endamebiasis

In a previous paper (1) I referred to amebic cases in three main groups. The division is somewhat arbitrary but serves as a working basis for clinical study. It further serves to help settle the question as to the results of treatment in the different types of cases in which the ameba may occur. Group 1 includes cases in which active symptoms of dysentery or hepatic abscess were manifested at the time of admission. Sixty of the 178 cases were in this group. Group 2 consists of 102 cases in which the chief complaint, or one of the complaints was intermittent attacks of diarrhea, sometimes alternating with constipation. Although the history of attacks of diarrhea suggests search for ameba, its presence need not be the cause of the abdominal complaints; a therapeutic test may be necessary to prove any

relationship. Group 3 shows sixteen cases in which the ameba was found without recorded history of dysentery. Three cases were of persons who seemed to be perfectly well and in whom the ameba was found incidentally as a result of stool examination. In three cases the patients were suffering from dermatitis and stools were examined for this reason. Eleven patients had normal or constipated stools; search for ameba was made because of indefinite abdominal complaints.

Group 1.—In this group of sixty cases proctoscopic examination revealed amebic proctitis in twenty and one of an indeterminate type of proctitis. In eight cases free hydrochloric acid was absent in the gastric contents after a test meal; in three of this group, bowel symptoms persisted after eradication of the ameba, but were controlled by dilute hydrochloric acid. In two cases the patients had abscess of the liver. Fifty-six of the sixty patients seemed to be cured; they had had two or more negative stool examinations at the conclusion of the first course of treatment. Three patients manifested a satisfactory clinical response but stool tests showed persistence of the ameba. One patient suffering from abscess of the liver died. The other patient with abscess made an uneventful and speedy recovery. When heard from three months later he had continued to improve and apparently there was no reactivation of the disease in the liver. Fifty-nine patients were advised to carry out further treatment at home. In this group there are known to have been fourteen recurrences. It is significant that ten of these fourteen patients had typical amebic ulcerations in the bowel, as determined by proctoscopic examination. One patient had an indeterminate type of proctitis which improved temporarily but recurred in four weeks. There was again improvement with the use of stovarsol and emetin. In the remaining three cases of recurrence there were no ulcerations of the rectal mucosa.

Group 2.—In this group of 102 cases, there are two cases of idiopathic ulcerative colitis (not amebic colitis) in which the ameba was found to persist after a course of treatment. In three cases of ulcerative colitis, the ameba seemed to have been eradicated. In all these five cases anti-amebic treatment was of some value. The important diagnostic point, however, is the recognition of ulcerative colitis associated with actual amebic colitis or, what is more common, the mere coincidence of the ameba which may play little if any part in the activity of the colitis. It is necessary to treat the amebic infection and at the same time suitable measures should be directed toward the other disease. In some instances the patient must be observed until the effect of the treatment of the amebic condition can be determined, and then if the colitis persists other treatment may be employed. In the remaining ninety-seven cases, there were nine recurrences. In six amebic proctitis was present and in three proctoscopic examinations were negative. Again the high incidence of proctitis in recurrent cases is noted.

The cure of eighty-eight patients in this group may be more apparent than

actual although reports thus far are encouraging. It is possible that the patients were less severely infected, or the factor of individual resistance may determine the amount of trouble that will result. Particularly in the cases without amebic proctitis it seems reasonable to expect cure. One case, however, illustrates the difficulty that may arise in the consideration of some cases in this group. The patient complained of attacks of abdominal cramps of an indefinite type associated with loose to watery stools. Roentgenograms of the colon and proctoscopic examination were negative. In the examination of the stool, *Endamoeba histolytica* was identified. As the ameba was the only tangible objective observation, stovarsol was administered and at the conclusion of treatment three examinations of the stool were negative. There was no subjective benefit from the stovarsol and further treatment with stovarsol was advised. The patient was seen again four months later. The abdominal cramps were unchanged. *Endamoeba histolytica* was again identified in the stool. A course of emetin was given and later a course of yatren. Neither drug seemed to affect the distress. In view of the presence of the parasite at the second admission it might be thought that the persistence of the parasite was the reason for the continuation of symptoms. I believe that the ameba bore little if any relationship to the complaints. As I have stated, in cases in which the ameba is related to or is the cause of the complaint, treatment has seemed to evoke a prompt clinical response. Even in cases in which the parasite persists at the conclusion of the first course of treatment or in which recurrence develops in even two or three weeks there is an immediate symptomatic response to specific treatment. On this basis the evidence does not seem sufficient to consider this patient's symptoms as due to ameba.

Group 3.—Most of the cases in which the ameba is found occur in this group. Unless a survey is undertaken or routine stool examination made, only a few such patients will come under observation for treatment. Of the sixteen patients treated, the three who apparently were well were free of the ameba. Two of the three patients suffering from dermatitis were apparently benefited. The parasite was eradicated in all three. Arsenic has long been used in the treatment of various types of dermatitis. These patients received stovarsol or treparsol. It is probable that the arsenic exerted a nonspecific effect rather than that the parasites played any part in the lesions of the skin. In conjunction with the Section on Dermatology in The Mayo Clinic types of dermatosis were treated in which not only *Endamoeba histolytica* but other intestinal parasites were present. The clinical results were disappointing and failed to establish any direct etiologic relationship between intestinal parasites and dermatosis. Four of the ten remaining patients in this group considered themselves definitely benefited. Seven were not clinically benefited. In none of the ten cases could the parasite be found on repeated examinations. It is difficut to evaluate the results of eradicating the ameba in the four cases, as

the other factors of correcting dietary errors, constipation and reassurance that a serious disease was not present, all must be considered before too much significance is attributed to the ameba. In a previous report (3) twenty-two patients of Group 3 were treated. There was no definite clinical benefit as far as the complaint was concerned in any of them. Combining the two series of sixteen and twenty-two patients, it is difficult to accept any conclusion other than that the presence of ameba in the absence of a history of diarrhea is not likely to bear any relation to the patient's complaints. An exception must be made in certain cases of abscess of the liver in which there is no history of diarrhea. Thirty-eight cases are much too few from which to make final deductions, but each year continues to confirm this impression.

Amebic Proctitis

Attention has been directed in this and in previous reports (15, 19) to the fact that patients suffering from proctitis are more likely to suffer from recurrence.

In this group the five cases with ulcerative colitis and the two cases with an indeterminate type of proctitis are omitted. This is for the purpose of more clearly discussing the problem involved in this group of cases. There were forty-one cases in Groups 1 and 2, which showed typical amebic ulcers as determined by proctoscopic examination. In sixteen (39 per cent) of the forty-one cases there were recurrences. For more accurate comparison the five cases of ulcerative colitis and the two indeterminate cases of proctitis are also deducted from the total number in Groups 1 and 2, which leaves 114 cases in which proctitis did not exist. Of this group of 114 there were seven (6 per cent) known recurrences.

Too much significance must not be attributed to the 94 per cent of cases without proctitis in which cure seemed to be effected. I believe that this percentage is high, but the important point is that the majority of the recurrences are in cases of proctitis. This strongly emphasizes the necessity of thorough treatment and long observation in such cases. In cases of amebic proctitis the infection must be from a more vigorous strain of ameba or else resistance of the host is lower than in the other cases.

The incidence of proctitis occurring in endamebiasis in the north temperate zone is probably more than from 6 to 10 per cent of the cases that have diarrhea due to the presence of the ameba. No significance can be attached to the forty-one cases (25 per cent) of the 162 cases in Groups 1 and 2 as an index of the incidence of proctitis as this is a selected group and represents only a part of the cases examined during a three-year period.

Conclusions

1. The organic arsenical compounds and yatren seem to be valuable additions to the treatment of endamebiasis.

2. At present, the most favorable results seem to be obtained from a combination of an arsenical compound and emetin. Auremetin by mouth may supplant emetin hypodermically except in very acute cases.

3. Simplification of treatment and an increase in efficiency are obtained by these methods.

4. Treparsol and stovarsol are equally efficient but since treparsol is rapidly eliminated, it would seem to be preferable to stovarsol.

5. Arsenic produces a small percentage of reactions. Indiscriminate usage of the drug is not without risk.

6. In cases with proctitis, recurrence is more probable than in those without gross ulcerative lesions.

7. Certain cases seem to be very resistant to treatment but persistence and variations in types of treatment should effect a cure in the majority of such cases.

8. Much is yet to be desired in the treatment of the persistent and chronic phases of endamebiasis.

BIBLIOGRAPHY

(1) Brown, P. W.: Nature, incidence and treatment of amebiasis. Jour. Am. Med. Assn., 1926, lxxxvi, 457-462.

(2) Brown, P. W.: Treatment of endamebiasis: especially with stovarsol. Illinois Med. Jour., 1926, xlix, 410-413.

(3) Clausen, S. W. and Jeans, P. C.: The distribution and excretion of arsenic after intravenous administration of arsphenamine in children. Am. Jour. Syphilis, 1922, vi, 556-567.

(4) Dale, H. H. and Dobell, C.: Experiments on the therapeutics of amebic dysentery. Jour. Pharmacol. and Exper. Therap., 1917, x, 339-459.

(5) Flandin, C.: Le dérivé formylé de l'acide meta-amino-para-oxy-phénylarsinique (tréparsol) dans le traitement de l'amebiase. Bull. méd., 1924, xxxviii, 1386-1389; Bull. et mém. Soc. méd. d. hôp. de Par., 1924, xlviii, 1628-1636.

(6) MacAdam, William: Report on treatment of various types of Endameba histolytica infection by the combined hypodermic and oral administration of emetin hydrochloride. Indian Jour. Med. Res., 1919, vi, 363-379.

(7) Gordon, R. M.: The treatment of amebic dysentery. Ann. Trop. Med. and Parasitol., 1923, xvii, 381-387.

(8) Marchoux, E.: Action du stovarsol sur le parasitisme intestinal. Paris méd., 1924, liii, 421-426.

(9) Martindale, W. H.: A note on emetin preparations for rectal and oral use. Tr. Roy. Soc. Trop. Med. and Hyg., 1923-1924, xvii, 27-45.

(10) May, Etienne: Un cas de mort par le tréparsol. Bull. et mém. Soc. méd. d. hôp. de Par., 1926, L, 1176-1178.

(11) Meleney, H. E.: Discussion. China Med. Jour., 1926, xl, 1090.

(12) Menk, W.: Weitere Erfahrungen über die Beeinflussung infektiörser Darmkrankheiten durch "Yatren" mit besonderer Berücksichtigung der chronischen Amöbenruhr München. med. Wchnschr., 1922, lxix, 1280-1282.

(13) Morgan, Julia: Notes on stovarsol poisoning. China Med. Jour., 1926, xl, 1086-1090.

(14) Osterberg, A. E.: A modification of electrolytic Gutzeit apparatus for the estimation of arsenic in biological material. Jour. Biol. Chem. 1928, lxxvi, 19-22.

(15) Stokes, J. H.: Modern clinical syphilology. Philadelphia, Saunders, 1926, p. 170.

(16) Turner, R. H. and Jones, P. H.: Yatren 105 in the treatment of amebic dysentery. New Orleans Med. and Surg. Jour., 1926-1927, lxxix, 233-237.

(17) Willmore, J. G.: The treatment of refractory cases of amebic dysentery. Tr. Roy. Soc. Trop. Med. and Hyg., 1923-1924, xvii, 13-26.

(18) Willmore, J. G. and Martindale, W. H.: The treatment of amebic dysentery by auremetine. Brit. Med. Jour., 1926, i, 525-527.

(19) Willner, O.: Remedies recently introduced in therapy of amebiasis. Medicine, 1927, vi, 341-374.

Chronic Pancreatic Disorders, Diabetic and Non-Diabetic*

By Anthony Bassler, M.D., F.A.C.P., *New York City*

THE importance of the pancreas as an organ in the economy is best expressed in the fact that a continuous loss of pancreatic fluid is fatal and death occurs in a few days after the removal of the gland. Compared to this continued loss of gastric juice, its absence, and even removal of the stomach, or the continuous loss of or blocking of bile, or loss of duodenal secretion, are without lethal effect.

Up to and since the work of Opie (2) but little in the way of investigation has been done in disorders of the pancreas (other than such as pertains to the islands of Langerhans, diabetes and insulin). Considerable effort has been spent to devise tests for estimating the external secretion, all of them being of little value for clinical work. Interest in such tests was cogent because examination of the stools for fat, muscle fibre, undigested nuclei and carbohydrates, and the urine and blood tests, too often were negative in the positive cases, and always negative in moderate and minor grades of disorders of the gland.

The value of duodenal intubation and the test (3) devised by me based upon its diastatic power has had application, and this with the new findings pertaining to the physiology of this enzyme (4) are the basis of this article. This test for pancreatic efficiency has now been studied for five years in practically fifteen hundred individual instances as well as in a considerable number of proven cases. The results of this large experience with the test now prove it to be a worth while method for clinical use, inexpensive and easily applicable for clinical purposes.**

There exists a stern necessity for research work on disorders of the inter-related activities of the pyloric function, secretions of the biliary apparatus, duodenal mucosa and detail as to portal absorption, liver storage, food oxidation and eliminations. Largely because so little is known of these factors in digestion, in which the functions of the pancreas occupy an im-

*Read before the American College of Physicians, New Orleans Clinical Week, March 8, 1928.

**Although the active principles of the thyroid and suprarenals are crystalline substances, insulin is either a colloid or intimately bound up with colloidal material. The same is true with the amylase (amylopsin) of the pancreas. It is interesting to observe that both of these active substances of the pancreas are recovered in this chemical form.

portant rôle, it is difficult to present clear pictures of clinical phenomena. Research work on the pancreas proves that this gland is as essential an organ in the body as the heart, liver, lungs and so forth, and like all essential organs has an independent function which continues at all hazards, and largely irrespective of emotional and often serious grades of disorders, however active they may be in depressing other secretions. Even with our lack of knowledge, and in spite of this dominance of function, disorders of external as well as internal secretions do occur; these apparently not always being due to organic diseases of the gland. It is only by assiduous studies in the future that these will be better known and classifiable in an entity sense. With the hope of stimulating further study and with no intention of being taken as definite, the following is submitted to serve as a classification. It must be remembered, as in chronic nephritis, that two or more states may co-exist:

Hypopancreorrheic states, functional.

Hypopancreorrheic states, consequent to infections of the biliary tract.

Hypopancreorrheic states, organic, non-diabetic.

Hypopancreorrheic states, organic, diabetic.

Hypopancreorrheic states, malignant and granulomatous.

In 1917 Wardell stated—"No symptoms are pathognomonic of pancreatic disease; an assemblage of symptoms indicate the probability of its lesion." To this we may add the most useful procedure in the test proposed by me. With these, a knowledge of the pathology of the pancreas and the biliary apparatus, and the means now at hand for diagnostic study of gastroenteric conditions, quite accurate work on the pancreas is possible.

Of the signs and symptoms that play in some of these cases the following may be mentioned: Asthenia, weakness, loss of weight, tumor (palpable or observed by X-ray in defect in the duodenum), so-called intestinal indigestion, indefinite pain, pressure sensations and tenderness in the center of the abdomen, anorexia, cyanosis from marked to very slight and transitory states, vomiting, more or less acute disturbance in the abdomen closely simulating an attack of gall stones, colic or perforation, constipation, diarrhea and jaundice. To these may be added the sympathetic ocular or Loewe's test (which is not dependable), the uncommon signs of defects of external secretion in steatorrhea and azotorrhea (all of which are late symptoms and most often are not found in the positive case), and those defects of the internal secretion in glycosuria, lowered sugar tolerance and the Cammidge reaction (all of which are helpful in the diabetic types, but fall short of being clinically useful or dependable so far as the condition of the whole gland is concerned). Any of these and many others may be helpful as additional points in diagnosis, but none individually, or all collectively are commensurate in value to the test recently advanced.

Hypopancreorrheic states, functional: The function of the pancreas is very rarely depressed for emotional reasons. The emotion must be of the

depressive type (and as far as I know be due to grief) and it must be sustained for days before deficiency of the pancreas will occur. When it does occur it is only transitory, and even though the emotion be continued, the organ resumes its function.

A woman of 35 years was in an automobile accident in which her husband and their two children were killed, she being wounded and shocked. For days she was in deep grief, took practically no food and slept little. On the fifth day she became ill, vomited and was prostrated. On the sixth day the test showed but 4 units. Two weeks later there were 16 units, and in six more days there were 18 units.

It may be that in the average type of continued fear and anxiety no effect on the pancreas will occur. In the instances here in which the test was made it was always negative. As stated before, apparently the pancreas is resisting the psychic and the usual emotions that will so distinctly affect the stomach, colon and kidneys.

Late in adynamic diseases when severe weight reduction has taken place, such as in pulmonary tuberculosis, cancer, yellow fever and Hodgkin's disease, the pancreatic function is very apt to be low, probably because of the general debility. Low unit readings have been found in the diseases mentioned. On the other hand, in several extreme cases of typhoid fever, ulcerative colitis and amebiasis, the units have been ample. It is probable that in some diseases the external secretion of the gland would be affected, yet in many lethal diseases it may not be interfered with at all in the life of the patient.

It seems logical to believe that the pancreas may run low in function in a reflex way. The instances in which this has been found most distinct are shortly after an attack of biliary colic from stones and in cardiac decompensation.

A woman of 42 years who had suffered from gall stones for years but had never had an attack of biliary colic was suddenly seized with one in which (because of the persistency of the pain—17 hours) an impacted stone with a hemorrhagic pancreatitis was suspected. She was not operated upon. On two examinations the units were but 2, and did not go above 4 until three days after all of the tenderness, nausea and anorexia had disappeared when the units were 10, and two weeks later 18, the latter two examinations being made on the tenth and fifteenth days after the colic had disappeared.

It is possible here that the low unit reading was due to some pancreatic depression of a transitory type. In all four cases of biliary colic that have been tested, three showed a low unit reading for a few days after the attack, and then became normal in one to three weeks time. There was one instance in which the units rose, but not to normal, subsequent to operation which proved an indurated pancreas.

Five cases of extreme degrees of cardiac decompensation were tested and all but one showed low unit readings with elevations taking place on improvement in the heart condition. The average cardiac case with mild degree of cardiac decompensation does not show a low unit reading, and it is possible that when a low unit reading occurs in the extreme case that it has a circulatory cause operating in the pancreatic blood vessels rendering the function of the gland deficient for the time being.

In the occasional case of arteriosclerosis seen, in which severe reduction in weight and strength has taken place, deficiency of pancreatic function should be suspected. In the diffuse form of this disorder and occasionally in the senile type, the vessels of the celiac axis may be markedly involved. When this is the case the pancreatic vessel is involved and thus the function of the gland will suffer. It is possible here that the loss of weight and vital exhaustion are due as much to this single item as any other. Four of such cases with units below 10 have been studied, three of which made substantial improvement in general health on frequent small meals and pancreatic feeding.

It is possible that the pressure of large pancreatic cysts may cause a deficiency of function. A case of small cyst was studied, the units being within normal range. Another case of small stones in the duct of Wirsung was observed, also with normal units. There now remains of this group a medley of cases which clinically, and because of deficient knowledge, can only be classed as functional, although it is probable that many of them are organic to some degree at least. In them various symptoms of digestive types and mainly intestinal in location are present. Among the symptoms collated are loss of weight, anorexia, nausea, excessive intestinal gas, vague pains here and there in the abdomen, constipation, diarrhea and others. When pancreatic estimations are routinely made, whatever the other diagnoses made, or causes for the symptoms are believed to be, here and there a low pancreatic individual is met with and one in whom dieting and pancreatic therapy are helpful. Occasionally one sees an individual in whom the diagnosis of biliary colic or even perforation is suspected because of the acuteness of onset and the intensity of the symptom of pain. Some of these are due to small isolated hemorrhages in the pancreas during which time the unit readings would be absent or low, the case recovering completely in a few days time.

A college boy 23 years of age was suddenly seized with an acute pain in the upper abdomen without contraction but with marked nausea and vomiting. He had no units in the test. It being deemed wise to open his abdomen for investigation, this was done thirty-two hours after the onset of the illness. Everything was negative except that his pancreas felt somewhat boggy. There were small hemorrhages descernible here and there along its course. The abdomen was closed without anything more being done and he made a smooth recovery. On the ninth day after the operation his units were 8 and on the twentieth day they were 14.

The above case, and two others of like kind that were not operated upon, suggest that there may occur very modified types of acute pancreatitis with slight hemorrhages which would throw the pancreas into abeyance of function for a short time, the condition recovering under simple medical treatment. Two instances of marked acute hemorrhagic pancreatitis that had been operated upon (one having a small pancreatic fistula that persisted) showed within six months after operation normal function of the gland.

Hypopancreorrheic states consequent to infections of the biliary tract: The gall bladder is rich in lymphatic ducts.

Some of these course to the liver, many of them empty in the glands about the bile ducts from which communication takes place into the pancreas and from thence to the lumbar glands. Infections and their toxemias from the gall bladder may be carried to the liver, bringing about congestion and fibrous formation in that organ, and from the ducts as well as the sac these often gain entrance into the head of the pancreas (a toxic lymphangitis), bringing about congestion, fibrous formation and even degeneration in the acinus cells, the latter sometimes extending into the islands of Langerhans. Enough anatomical, medical and surgical evidence is on hand to prove that the pancreas can and often does become affected from gall bladder conditions. Taking up the study of gall bladder disease from the standpoint of the activity of the pancreas, as to how often and to what extent it causes interference with the pancreas, and reversely studying gall bladder diagnoses from estimations of pancreatic activity some quite worth while new clinical data have now been collected.

In a series of gall bladder abnormalities verified by operation, the average figure is 6 1-5 units, and of those in which stiffening of the pancreas was noted 2½ units is recorded. Surgeons have reported pancreatic stiffening in from 5 to 20 per cent of gall bladder operations. The personal equation of surgeons and degree of care in the examination of gall bladder cases varies distinctly making statistics almost worthless. In my series, the pancreas was considered stiffened before operation in 67 per cent and negative in 33 per cent. Of these all who had pancreatic hardening (usually of the head alone) showed low units, and in those in which it was negative the units were normal or above. In this series the Meltzer-Lyon method of examination was positive in 45 per cent and negative in 55 per cent. Added to these were the non-verified cases of cholecystic and duct disease in all of which the units were less than 10 with only 36 per cent having normal or above normal figures. In these, compared to the verified cases, strangely enough the Meltzer-Lyon was positive in 60 per cent and negative in 40 per cent. While the diagnosis might have been in error in some of the non-verified cases, positive Meltzer-Lyon tests were lower in those in which distinct pathology was unquestionable. On the basis of these findings the history, physical examination, cholecystography and icteric tests were employed for diagnosis, the Meltzer-Lyon test being discontinued and the pancreatic test employed to diagnose pancreatic stiffening. The latter was considered important to separate the surgical from the medical cases of cholecystic disease and to serve as a means of further study of the cholecystectomized individuals who returned with original symptoms and in whom adhesions and retained stones did not seem to answer as the cause.

In the year of 1925 one hundred instances of cholecystectomy done for stone and non-stone conditions studied after operation, showed fifty-one returns with symptoms, often the exact duplicate in intensity or in modified forms of those present before operation. Other than in those who had had attacks of biliary colic (in which

the post-operative result was almost perfect) the difference in the stone and non-stone cases was not marked in favor of either one from relief of symptoms. In 1926 and 1927 pancreatic efficiency was studied routinely. In all there were three hundred and ten cases of supposed gall bladder disease, and grouping the stone and non-stone cases together, sixty-two were operated upon, cholecystectomy being done. There were five cases in which a mistake in the provisional diagnosis was proven and two deaths. Of the fifty-five confirmed cases the test showed the pancreas below normal in thirty-nine, and of these the pancreas was definitely stiffened in thirty-four. Of these fifty-five cases but six returned with symptoms simulating the former ones, a reduction of from 51 per cent of failures in 1926 to about 9 per cent, which in my opinion was due to the value of the pancreatic test in discerning the case which has a "hit of the pancreas", functional congestive or fibrous, and which always convicts the case as a surgical one in the first instance and positively after a course of treatment if the pancreas does not enhance in efficiency. In the six that returned with symptoms, together with thirty-seven more that had been cholecystectomized before I saw them, some very interesting clinical data were gained. Reporting on the six above referred to, five had a stiffened pancreas at operation and one was reported as negative. Numerous tests were made on the first five after operation, proving the pancreas to be always low, and all of these did well symptomatically on alkalies, pancreatic therapy and diet. In the thirty-nine cases in which the units were low and excepting the six mentioned, it was proven that after cholecystectomy the pancreas became efficient in from three weeks to three months time. In the six mentioned the sac was removed too late and the pancreas had already become fibrous; thus, in operation for gall bladder pathology in which a distinct stiffening of the pancreas is noted, one should be a little guarded in a prognosis of positive relief of symptoms. Disorders of the pancreas alone may give symptoms that so closely simulate gall bladder pathology that differentiation between the two clinically is not possible and cannot be made until the gall bladder has been removed and the pancreas tested. After operation if symptoms return the pancreas should be considered as a factor of cause, as well as adhesions and retained stones, and the pancreas should be tested after operation in these cases for a pancreatic solution of the cause of symptoms as well as before operation to help separate the surgical from the medical type of case. It may, therefore, be noted that since the test became routine in gall bladder work the percentage of operations on the whole has lowered in favor of medical handling, as well as the percentage of success in operation. Individual instances of each of the above are represented in deductions in the following in which there were numerous instances, some of which have already been reported (5):

In March, 1924, a woman of 54 years complained of symptoms due to menopausal arthritis. She began to lose weight and strength in the latter part of 1926. Four pancreatic tests showed 2 units. In Febru-

ary, 1927, she became jaundiced with distinct symptoms of gall stones. On the day before the cholecystectomy was done (April, 1927) her units were still 2. The gall bladder containing stones was removed and the pancreas was found to be hard. Nine weeks later her units were 10 and in the fourteenth week there were 14 units.

Note: Gall bladder disease with congested pancreas and restitution of pancreatic efficiency.

A man 39 years of age had distinct history and findings of gall stones. His units regularly were 4 on several occasions. Cholecystectomy was done; stones and stiff pancreas found. His pancreas was tested over a year's time, the units always remaining 4. By dieting and pancreatic feedings his complaints were controlled and his general health held up, but there could be no let-up on these for more than a period of five days. Lately sugar has appeared in his urine at times when he has not taken pancreas.

Note: Gall bladder disease, operated upon too late to save the pancreas and obviate a possible diabetes. Chronic pancreatitis.

A woman 44 years of age with warranted history and suggestion of gall stones was operated upon, cholecystectomy being done and no stones were found on operation. No report possible on condition of pancreas, operation being performed eight years ago. Clinical symptoms similar to those before operation continued over the intervening years. Pancreas 2 units. Diet, alkalies and pancreas therapy most helpful. Occasional glycosuria.

Note: The case was either an infected cholecystitis causing persistent fibrous pancreatitis, or as is more probable, an original diseased pancreas with symptoms simulating gall bladder pathology.

Hypopancreorrheic states, organic, non-diabetic: This heading is used to encompass a group of indefinite cases and the few in number that are more definite in smyptoms. Operations and postmortems show that induration and nodulation of the head of the pancreas are found in 80 per cent of all adults. It is true that in the vast majority of these no symptomatic evidence of pancreatic inflammation or involvement exists, or at best it is so obscure that the pancreas is not thought of in its production. In them the more definite signs and symptoms already mentioned commonly do not exist, yet there is little doubt but that there is significance in the vague and colloquial digestive symptoms often present. Omitting from consideration such cases as definitely characterize the cholelithic, those secondary to malignancy and diabetic cases, and presenting only what may be termed the dyspeptic, one can divide the symptoms here into two groups, local and general.

Local: The special feature of these symptoms is that they more particularly are intestinal rather than gastric and have already been described under the functional types. All of the digestive symptoms represented in many different types of cases have been seen.

General: Of this group the most conspicuous symptoms are loss of weight and difficulty in restoring and retaining it. To this, of course, should be added a train of neurotic, neurasthenic and more or less handicapping or partial invalidism states.

The most definite instances of this type are those due to persistent fibrous changes from neglected gall bladder pathologies, and those which accompany malignant or granulomatous diseases of the pancreas itself.

The diagnosis here should be arrived at by the presence of symptoms suggesting pancreatic disease in addition to the pancreatic test, or the test alone carefully performed; stool and urine analyses are sometimes helpful. A word on therapy is worth while here. Late in the disease of inter- and intralobular pancreatitis but little can be done, but before this stage much help may be brought about by diets that sharply control the starch intake with complete hydrolysis and dextrinization. The ingestion of from 100 to 250 grams of pickled pancreas a day, a good quality of pancreatic powder in larger than usually given doses and the triple strength enteric-coated pancreatin tablets as suggested by Sansum and put up by one of the pharmaceutical concerns, with or without fair sized doses of some of the alkalies may be effective.

Hypopancreorrheic states, organic, diabetic: Attention has repeatedly been drawn to the incidence of diabetes in gall bladder disease and to the frequency of gall bladder conditions in diabetes. Joslin particularly has drawn attention to this (6) and I have seen one case that became sugar free two months after cholecystectomy for stones was done and which has remained so on a generous diet up to the present, now nineteen months. Surgeons have reported the incidence of glycosuric states in gall bladder disease, Deaver having reported 5 per cent in a large series. These facts, with the incidence of involvement of the pancreas in gall bladder diseases, and now the findings with the pancreatic test, show distinctly that pancreatic disorder secondary to gall bladder pathology must always be searched for in the story of diabetes. Since gall bladder diseases are so much more numerous than instances of diabetes, and diabetes may exist without stiffening of the gland, the reason for the greater incidence of glycosuric states in gall bladder disorders is perhaps explained in that there are fewer islands of Langerhans in the head than in the body and especially in the tail of the gland. Injury to the head of the organ as a result of infection of the gall bladder is presumably less constant in the production of glycosuria than in true diabetes, and probably this has something to do with diabetes which is associated with gall bladder diseases being more mild than the average case of diabetes. Joslin has repeatedly said—"If one could pick out the best kind of diabetes to have one would pick out gall stone diabetes."

Working on the suggestion of what may be called for distinction—true diabetes, the external secretion of the pancreas was studied to see if it would show a change from normal. Fifteen cases of well confirmed diabetes were studied. Of these two had high normal units (20 units each) and two were slightly less than normal (8 units each). In all the rest the units ranged from none to 6. The average unit reading in all was 5 3-5 with 3 1-5 units in the main 13. Thus the units were below normal in 86, 33 per cent of all and normal in 13, 13 per cent. At once this is a striking finding, especially in that the two who had high pancreatic readings were easy cases to control dietetically, while all of the rest required insulin in large or small

doses. If this finding is confirmed it promptly brings up the interesting query as to how much of a digestive disorder diabetes is, as well as how much is it only a metabolic one? May not a factor be that because of deficiency of the external secretion of the pancreas, the molecularly proper end sugars for glycogen storage in the liver and muscle cells are not manufactured to completion of intake, and thus, being more or less foreign to the tissues, they are incapable of storage and flow over into the blood stream? Such incomplete sugar is still capable of oxidation by insulin or complete elimination from the body. It is considered that the islands in function are more or less apart from the acinus cells and that diabetes is only an island affair. But pathology in diabetic cases shows that usually the whole gland is involved, and if only the island cause is considered (as seems to be generally held) how is it that in gall bladder diseases (which causes a general pathology in both cells and mostly in the head where the acinus cells predominate) that glycosuria is so often met with?

In our group of thirteen severe cases, attention directed to the external secretion of the gland evolved most striking results in reduction of insulin units with benefits in general health taking place. It has been reported elsewhere (4) that in five of these there was much difficulty in holding the urine sugar free on diets which approximate basal metabolism without considerable sized doses of insulin. In all of them when put on pancreatic feedings in doses of from 100 to 250 grams a day, from about the second or third day on, a marked reduction of insulin with distinct general improvement in health, strength and well being took place in each case. In four others this result was not so striking in insulin reduction but in nine of them it was definite. In the other four no worth while result could be noted, these four strangely enough having three in which units were relatively high—4, 4 and 6, and but one with no units. With experience in six more recently studied cases I am now of the belief that the external secretion of the pancreas cannot be totally neglected as it has been in the past in handling diabetic cases. The external secretion of the gland has a distinct significance etiologically, diagnostically and therapeutically.* This is not true in all instances of diabetes, but it certainly is in a large enough proportion of cases to be most important. No instances of hemochromatosis were studied, these being considered as a too irregular type of diabetes because of liver and iron metabolic disturbances.

Hypopancreorrheic states, malignant and granulomatous: Of cancer, sarcoma, syphilis and tuberculosis, cancer is the most common. All excepting sarcoma occur mostly in the head of the gland, and it is because the pancreas to its so-called neck comprises the largest portion of the gland and is the part mostly concerned in the external secretion, that lowered or absence

*Argument has been presented that in pancreatic feedings the islands of Langerhans (and thus insulin) are ingested. If insulin is destroyed in the stomach this cannot prevail, and at best the amount that would be taken would be too small to accomplish the results observed.

of deficiencies would be met with in these conditions.

As far as is known, no instances of tuberculosis have been encountered, although it is possible that the not uncommon miliary tuberculosis of the pancreas associated with acute or chronic tuberculosis was met with in one instance which was absent of units. The pancreatic efficiency here is usually low in the advanced case because chronic pancreatitis is not an uncommon associate of tuberculous lesions of other organs.

Syphilis of the pancreas is found in about one-fourth syphilitic newborn infants, and the pancreas is rarely the seat of gummata occurring in the acquired form. It is most probable that acquired syphilis only very rarely causes chronic pancreatitis.

Cancer of the pancreas may occur anywhere in the gland, but is twice as frequently confined to the head as in the whole gland or other localized parts. Those of the head and whole gland comprise about 94 per cent of all instances, and it is most probable that deficiency states of external secretion are the rule. In the two instances studied both were totally hypopancreorrheic on several tests in each.

Sarcoma was met with in one instance, it involving the tail and the body. In this instance normal units were present, probably because the head was not involved. No instances of adenoma were met with.

Conclusions

The author's pancreatic test has been employed in over fifteen hundred patients and has been found to be useful clinically. The best stimulant is peptone solution and one of magnesium sulphate serving as a fair second providing bile flows. Practically all of the tests used formerly are of little value clinically, most of them being positive in negative cases and negative in positive cases.

A practical classification of hypopancreorrheic states is offered.

The pancreas is a most essential organ in the body and one which is not easily affected by functional neurological or reflex disturbances.

Reduction in its function occurs in some diseases and not in others. It is a factor of importance in cardiac decompensation, arteriosclerosis and some types of digestive disturbance.

In the cases of acute abdominal disturbances isolated hemorrhagic pancreatitis is worthy of inclusion as a subdivision entity of acute hemorrhagic pancreatitis.

Infections of the biliary tract often cause dysfunction of the gland, and the pancreatic index should be studied in all such cases. When uniformly low, "stiffening" of the head of the gland should be suspected, and in the stone as well as the non-stone cases operation is called for in most of these instances. After cholecystectomy with a return of symptoms the pancreas should be considered as a causative factor and the efficiency of the gland tested.

Internists and gastro-enterologists should consider disorders of the pancreas as a cause of digestive symptoms and adopt appropriate treatment where hypopancreorrhea exists.

The external ability of the pancreas should be studied in diabetics. In 86

per cent of our cases this was deficient, and this deficiency is an important factor both etiologically and therapeutically in the handling of the diabetic.

In malignant and granulomatous states it depends upon how much of the head of the gland is involved as to whether the external secretion would be deficient or not.

(1) Waters and Bollman: American Medical Association Journal, November 26, 1927. Vol. 89, p.p 1847.

(2) Opie, Eugene L.: Diseases of the Pancreas, Cause and Treatment.

(3) Bassler, Anthony: Archives of Internal Medicine, February, 1925. Vol. 35, p.p. 162-174.

(4) Bassler, Anthony: Archives of Internal Medicine. Ibid.

(5) Bassler, Anthony and Lutz, J. Raymond: Medical Journal and Record, September 2nd and 16th, 1925.

(6) Joslin, Elliott P.: The Treatment of Diabetes, p.p. 476-477.

Present Results and Outlook of Diabetic Treatment*

By Frederick M. Allen, M. D., *Pyschiatric Institute, Morristown, New Jersey*

DIABETES is a subject of perennial interest. The topic selected for me is in the nature of a review, which is timely, because at present we have reached a point where some old questions are apparently decided and new ones are just beginning to be opened up by research.

Diet

The first part of diabetic treatment is necessarily diet. This is the most important and fundamental part, and the only one which must be employed in every case. The components of the diet requiring consideration are protein, carbohydrate, fat, and finally total calories and body weight.

Protein has been the subject of past disputes which now appear to be settled. Various authors have claimed that protein is specifically toxic for diabetics, possibly even more harmful than carbohydrate, and that it should be limited to very low quantities in the diabetic diet. These contentions were never proved and may now be regarded as definitely exploded. There is no specific toxicity of protein for diabetics, and no influence beyond its caloric value and its content of potential carbohydrate. It need not be closely restricted in diabetics who are free from kidney diseases or other special complications. It should on the contrary be used fairly liberally, because it gives strength and adds taste and variety to the diet. In our closest restrictions in uncomplicated cases without insulin, we never use less than 60 grams of protein for the permanent diet, and habitually use as much as 80 grams. In milder cases or for persons especially fond of protein, it is possible to raise the allowance to 100 or even 120 grams per day, seldom more. The form in which the protein is given is considered immaterial.

Carbohydrate has been subject to wide extremes of variation in the past, ranging from almost complete elimination in the classical diets to the almost exclusive carbohydrate rations represented in oatmeal and related "cures". Similar divergences have continued almost to the present time. In the high fat diets which were recently prevalent, carbohydrate was limited to the least possible proportions, perhaps 30 to 60 grams per day. On the other hand Sansum has shown that patients under insulin treatment may sometimes receive quantities up to several

*Read before the American College of Physicians, New Orleans Clinical Week, March 8, 1928.

hundred grams of carbohydrate per day with no great increase in the insulin requirement. Our own practice is intermediate in this respect, allowing seldom less than 50 grams of carbohydrate in the permanent daily diet of a patient without insulin, and more often about 80 grams as a rule. In milder diabetics or under special conditions the carbohydrate may be increased to 100 grams or even higher. The reason for avoiding the highest proportions of carbohydrate is not that the insulin requirement is unduly raised, but rather that the fluctuations of sugar are too marked. A smooth regular control of the blood sugar is more readily achieved when the carbohydrate is limited as mentioned.

Fat furnishes the greater part of the calories in all standard diabetic diets, and the so-called high fat diets merely carry the use of it to an inconvenient and harmful extreme. These diets, which recently were a fad widely prevalent in this and other countries, were based upon the belief that fat is harmless in diabetes, or that the diabetic tolerance is affected only by preformed carbohydrate and by the potential carbohydrate which forms about 60 per cent of the protein molecule and a small part of the fat molecule. It is justifiable to say definitely that this belief is false, because it was never supported by any proof and complete proof to the contrary has been published. The diabetic patient requires regulation of every kind of food, including fat. When protein and carbohydrate are supplied in the amounts already mentioned, we complete the diet with sufficient fat to make up the requisite number of total calories.

The total calories are the most important factor in the diet treatment of diabetes. This factor is practically synonymous with the body weight, since the number of calories supplied governs the weight of the patient. Before the discovery of insulin, the importance of this principle was demonstrated by the fact that cases which were too severe to be controlled by the former methods could be brought and kept under control by fasting and undernutrition. Since the discovery of insulin, this fact has received mathematical proof. For such an experiment it is best to choose the severest cases with the highest insulin requirement, so that the insulin supply is derived as far as possible from our own injections and as little as possible from the variable source of the patient's own pancreas. If the total calories are kept the same, it will be found that only a slight change in the insulin requirement results from varying the carbohydrate allowance from 30 grams to as much as 200 or 300 grams per day. On the other hand, if the total calories and body weight are increased by the addition of fat or any other food, the insulin requirement rises tremendously. The most important precaution for the permanent control of diabetes is therefore the regulation of the total calories and body weight. The obese patient practically never requires insulin, because by reducing the weight to normal we change the diabetes to a mild form. If the insulin requirement of any patient is excessive or if the fluctuations of sugar cannot be controlled, we can reduce the insulin and

generally obtain smooth control of the sugar merely by reducing the body weight by suitable changes of the total calories.

The great majority of cases must be treated by the general practitioner, but no physician should undertake to treat diabetes unless he can calculate a weighed diet. The majority of cases do not actually require weighed diet, because of their mildness; nevertheless, in order to advise intelligently concerning the composition of an unweighed diet, the physician should possess the knowledge of weighed diets and should take care that the ration advised for his patient is properly balanced and not too high or too low in any components. Merely to prohibit sweets and high starches may stop glycosuria for the time being but nearly always results in relapses or other trouble later. When the diabetes is more severe, a weighed diet becomes essential. When it is severe enough to require the use of insulin, the diet should invariably be weighed, unless in rare instances the patient becomes able to estimate his food almost as accurately as if it were weighed.

The mere calculation of accurate diets is a simple matter, and owing to its importance it should not be complicated with any superfluities which will make it more difficult for the general practitioner.

There has been something of a fad in the use of respiration apparatus, and if a thyroid disorder is present or suspected the determination of the basal metabolism may of course be instructive. But for the treatment of any ordinary cases of diabetes it should be understood that respiratory determinations or basal metabolism tests are unnecessary. There is no reason for planning an initial diet according to the basal requirement. There is no accuracy in determining the basal rate and then guessing at the calories needed for exercise. One may as well guess at the entire requirement in the first place. It is best in the majority of cases to undernourish the patient more or less at first, while sugar and acetone are being cleared up. The diet is increased slowly or rapidly according as the patient happens to be over or under normal weight. In the long run the number of calories needed is determined by the body weight. A diet on which a patient continues to lose is insufficient. A diet on which he continues to gain is excessive. The right diet is the one which permanently maintains the desired weight. This rule is simple, but there is no ultra-scientific substitute for it.

Another of the recent fads, namely the calculation of the so-called ketokenic-antiketogenic ratio, is likewise unnecessary. This practice arose from a false view of diabetes, namely the belief that only carbohydrate affects the diabetic tolerance. In other words, the strain upon the pancreatic function was supposed to be measured by the total potential carbohydrate of the diet, consisting of all the preformed carbohydrates, plus about sixty percent of the protein, plus about ten percent of the fat. Fat was imagined to be harmless except for the production of acidosis. The ideal diet was then conceived to be the one which would supply the highest nutrition in the form of fat calories without giving rise to

acidosis. The purpose of calculating the ratios between the fatty acid and carbohydrate components of the diet was therefore to supply a maximum of the former with only such a minimum of the latter as was necessary to prevent acidosis. This doctrine was never supported by any proof, and it disregarded the complete disproof which already existed in the form of experiments published in conclusion with the undernutrition treatment. The introduction of insulin furnished a further means of exposing the fallacy as above mentioned. When the total calories are kept unchanged by substituting carbohydrate for fat, it is an easy matter to confirm Sansum's recent reports by demonstrating that the carbohydrate allowance may be varied widely with surprisingly little change in the insulin requirement —sometimes no change at all. On the other hand, when the total calories are greatly increased by adding fat, and especially if the body weight is thus markedly increased, the increase of the insulin requirement may be slow and gradual but it becomes enormous. We thus return to the fact which was proved years ago, namely that the total calories and body weight are the chief factors determining the insulin requirement or the burden upon the pancreatic function. Neither fat, alcohol, nor any other source of calories is harmless or can be disregarded. The purpose of limiting fat is not merely to prevent acidosis but to limit the total calories. There is no reason ordinarily to restrict protein or carbohydrate to an extreme minimum. As mentioned, I do not generously favor the extremely high proportions of carbohydrate, because the fluctuations of blood sugar are harder to control. But for certain special purposes this information is of great value; for example, in giving a diet consisting chiefly of carbohydrate to a diabetic with cirrhosis of the liver. Ordinarily, what is desired is a rationally and agreeably balanced diet. There is considerable leeway for individual preference, so long as the total calories and body weight are suitably regulated. With any possible proportion of protein and carbohydrate that may be chosen under the principle here explained, the occurrence of acidosis is impossible, and ketogenic-antiketogenic ratios should be forgotten.

Insulin Treatment

Though insulin justly ranks as one of the greatest discoveries of medical science, its use should be avoided whenever possible. This advice is not based on any danger in insulin, for there is no danger which should deter anybody from using insulin when it is actually needed. The danger of hypoglycemia has been exaggerated. It is a discomfort or even a distressing affliction to the patients and families in a small proportion of specially difficult cases. A few deaths have been reported from this cause, but as a rule under avoidable conditions. We have had no such fatalities in our entire series of cases, and the chance of such is trivial in comparison with all the other dangers of diabetes.

The reason for avoiding insulin treatment is its inconvenience. It is a mistake for patients to think that by taking insulin they can avoid a strict or weighed diet. The need of an ac-

curate diet is increased by insulin. Under treatment by diet alone, only glycosuria or hyperglycemia is to be feared. The patient may estimate or vary his diet at will so long as he keeps it low enough. A slight excess may be balanced by extra strictness preceding or following it. With insulin there is the additional risk of hypoglycemia, and the general results are poor unless the diet is kept rigidly exact and uniform.

Insulin should never be given to obese patients, unless temporarily for some special purpose, because the simple reduction of the weight to normal will nearly always convert such cases into a very mild and easily managed form. As a general rule in other cases, if moderate undernutrition will control the diabetes, it is preferable to keep the patient a few pounds below the average normal weight than to burden him with insulin injections. The chief exception is in children, for even if their diabetes is in a mild incipient stage, they are generally safest with a little insulin as a precaution against progressiveness. Also in some border-line cases in adults, when the patient is barely getting along with uncomfortable privations in the attempt to avoid insulin, it is sometimes helpful to give insulin for some period, because the more thorough pancreatic rest thus afforded ass'sts the gain of tolerance, and paradoxically in some instances the temporary giving of insulin is the means of permanently avoiding it. But whenever the diabetes is sufficiently severe, and management by diet alone entails any serious degree of emaciation, disability or discomfort, insulin should be resorted to without hesitation.

We still adhere to the ideal of keeping the urine sugar-free and the blood sugar normal at all times. This involves questions of the total dosage and the number of injections per day. It is best to regulate the diet and body weight, as already stated, so as to keep the total dosage as low as possible. The number of injections may thus be reduced in the milder cases. In the more severe cases the fluctuations of sugar, the alternations of glycosuria and hypoglycemic attacks are much less troublesome when the total dosage is kept low. The number of injections into which the day's dosage is divided in any case can partly be predicted from experience, but largely must be determined by trial. In the milder cases one injection, usually at breakfast time, may suffice. With increasing severity the point is reached where increase of the single dose no longer gives ideal control of the sugar; either glycosuria or hypoglycemia occurs. The required insulin must then be divided into two doses, usually given at breakast and supper. With still greater severity, three doses may be needed, and in rare juvenile cases four doses. In this connection two practical rules of insulin action may be remembered. The larger the single dose of insulin, the less is the effectiveness of each unit in it. The greater the number of injections in a day, the smaller is the total amount of insulin required.

The chief difficulty encountered, especially in the severest youthful cases, is the tendency to hyperglycemia or glycosuria toward morning, and to hy-

poglycemia toward evening. Members of the Toronto school first introduced the practice of givng insulin with meals, thus crowding all the insulin usually into eight to twelve hours and leaving a long night period of 12 to 16 hours without insulin. The suggestion of concentrating most of the carbohydrate in certain meals does not obviate the difficulty in severe cases. In general, it should be remembered that there is no fundamental reason for giving insulin with meals. Insulin is needed for the metabolism of food, not for digestion. It is therefore required through the entire 24 hours. Also I called attention long ago to the fact that the insulin requirement is not correlated with the mere level of metabolism. For example, heavy exercise raises total metabolism and lowers the insulin requirement. (Incidentally, this again illustrates the folly of beginning treatment by prescribing a "basal" diet and minimal activity in order to keep metabolism lower.)

Apart from intentional experiments, it will sometimes be noticed that a child on a constant program of diet and insulin will show glycosuria on a rainy day with quiet life, and hypoglycemia on a bright day with strenuous play. Ignorance of this simple principle seems to have been responsible for the misconception that the lower metabolism during sleep at night should be accompanied by a lower blood sugar and a smaller need for insulin as compared with the active day period.

In milder cases insulin may be given with meals as a matter of convenience, and with this assistance the patient's own pancreas will tide over the interval without injections. But in the more severe cases referred to, the rise of sugar during the night should be prevented by more equal spacing of the doses. In rare instances, there is no way of smoothly regulating the sugar except by a fourth dose of insulin about midnight. Nearly always, however, it is sufficient to shorten the night interval by giving the morning dose 30 to 90 minutes before breakfast (or as early as possible without causing hypoglycemic attacks) and the evening dose an hour or two after supper or at bedtime. The exact details must often be worked out by trial in the individual case.

By means of insulin in conjunction with proper diet, it is theoretically possible to enable every diabetic, in whom fatal complications do not already exist, to live out his full natural lifetime. Specialists and all others who write on this subject in medical journals invariably describe the life-saving effects of insulin in all types of cases. Yet it has been one of the most unpleasant surprises to find that diabetic mortality figures published both in this country and in England have shown no fall since the discovery of insulin. The reason must evidently be sought either in a failure of physicians at large to use insulin properly, or a failure of patients in general to follow the instructions properly. The remedy for this condition seems to be largely a responsibility of the general practitioner, who should either control his diabetic cases effectively or refer them to somebody who will do so. It is sufficiently demonstrated that the careless or unskilled use of insulin

does not save diabetic lives in the long run.

Treatment of Complications

The chief complications requiring consideration are acidosis, gangrene and infections. The most important treatment is prophylactic, for if all cases of diabetes were well controlled from the outset there would be practically no diabetic coma or gangrene. Under existing conditions it should be emphasized that now, as formerly, these complications are the chief causes of death in diabetes.

Acidosis

There is little new to say on the treatment of coma, present or impending. Most important is the use of maximum doses of insulin, often amounting to more than 200 units in 24 hours. Only second to this is the administration of the largest possible quantities of fluid, because the tissues in acidosis are dangerously desiccated and because water is needed for abundant diuresis. Fruit drinks are usually preferred for this purpose, because they can be taken in large volume with the least tendency to nausea, and because they also supply carbohydrate. Coffee or tea with sugar, or anything else that will furnish water and carbohydrate acceptably, may be used. There seems to be some perplexity as regards the need of supplying sugar to a patient who is already overloaded with sugar. But we wish to use insulin in huge doses and the plentiful administration of sugar is a safeguard against hypoglycemia. For the immediate time we have no interest in stopping glycosuria, but only in stopping acidosis; provided enough water is present the excess of sugar is harmless and even makes a useful diuretic. In particular, according to the laws of metabolism, increased sugar supply makes increased combustion, and in this way also the giving of sugar assists in getting rid of acetone. If the patient's stomach is unable to retain fluid to the extent of 5 liters or more in 24 hours, saline or glucose solutions should be given rectally and intravenously. Hypodermoclysis requires rigid asepsis to guard against the serious danger of infection. Intravenous injections carry no such danger, and in a critical case, in preference to delaying several hours, it is justifiable to inject a clean filtered solution intravenously without sterilizing, because infection never results. But the volume of intravenous fluid should be gauged with regard to the strain upon the weakened heart. Alkali is less important since the introduction of insulin, but my personal belief is that sodium bicarbonate is helpful in moderate dosage, (5 to 20 gm. total) in cases with much reduction of the plasma bicarbonate or much dyspnea. Keeping the patient warm, emptying the stomach or bowels, and attention to any infection or other complications, are routine measures according to conditions. Most drugs are useless; caffein, digitalis, or other cardiac stimulants may be indicated because of the grave circulatory factor in severe cases, but it is questionable whether they can often change the outcome.

A frequent cause of death nowadays is the form of acidosis which often occurs suddenly in insulin-treat-

ed patients who have glycosuria. It commonly begins with abdominal pain and vomiting and progressive weakness, and the classical symptoms of dyspnea and dim consciousness may not be manifest until a hopelessly fatal stage has been reached. A differential diagnosis is sometimes necessary between this condition and a hypoglycemia attack, one demanding insulin and carbohydrate, the other carbohydrate without insulin. The distinction is readily made by the symptoms, and by the finding of high sugar and acetone in the urine or (if the kidneys are highly impermeable) in the blood. Incidentally, the nitroprusside test of the blood plasma, which can be performed at the bedside if necessary, is probably the quickest and surest index of the condition and progress at the various stages in any type of acidosis.

The time element is so vital in combating acidosis, that one of the most important phases of the treatment may be that which is prescribed by telephone, in instances when there may be a delay of an hour or more before the doctor can reach the bedside. The history and description of the symptoms often suffice for a diagnosis, which is further strengthened if a member of the family tests the urine for sugar and reports it heavy. Sometimes insulin is available and a dose of as much as fifty units can be ordered immediately. Under any circumstances the forcing of fluids and carbohydrate can be started. Regarding insulin, a well-informed physician could rarely make a mistake which would involve any actual danger if he were to arrive within an hour or two to give antidotes in the form of sugar or epinephrin if needed. On the other hand, every delay in beginning treatment will involve an appreciable increase in the mortality of acidosis. When too long a time elapses the patient reaches a fatal stage, in which strenuous treatment may clear up sugar and acetone and raise the blood alkali, but death nevertheless occurs with symptoms resembling shock.

Diabetic gangrene has a double basis, namely, a specific deficiency of healing power in the tissue, and deficiency of blood supply due to arteriosclerosis. Sometimes only one of these causes is present. For example, diabetics with uncontrolled sugar are subject to local infections, necrosis, and septicemia from trivial injuries in the lower extremities or any part of the body, and the term gangrene is applied to many of these conditions in a loose sense. Also, true gangrene may rarely develop in a diabetic whose blood sugar is kept fully normal under treatment, merely because arteriosclerosis is present to an extent that will cause gangrene also in a non-diabetic. The rarity of this occurrence must be emphasized, because the onset of gangrene in a diabetic without glycosuria is generally explainable by the presence of hyperglycemia, and this is one of the reasons for insisting upon normal blood sugar even in the elderly. The development of arteriosclerosis in diabetics may be of interest in connection with the involved problem of the etiology of arteriosclerosis in general. It is present in every diabetic who has had active glycosuria for a sufficiently long time—perhaps

10 years, more or less. Even with the mildest diabetes, in which the patient may make light of his glycosuria because it goes on seemingly with no symptoms or harm for a seemingly indefinite time, arteriosclerosis is inevitable, and the patient should be warned that his arteries are thickening year by year and he is becoming more liable to gangrene and other vascular complications. After the circulation has become seriously impaired, for example when examination shows that pulsation in the dorsalis pedis artery is feeble or absent, it becomes important to insist on strict cleanliness, warmth and general care of the feet, and the utmost avoidance of the slight injuries (abrasions, trimming of corns, etc.) which afford the commonest starting points of gangrene. But the diabetes should be emphasized as the great cause back of everything, and when the sugar is thoroughly controlled before the arteries have become too badly occluded, other precautions may be disregarded because there is no greater tendency to gangrene than in a non-diabetic.

The medical treatment of gangrene is by diet, aided usually by insulin. The best diet is one consisting largely of protein and carbohydrate, for example, 50 to 80 gm. protein for maintaining strength, 80 to 120 gm. carbohydrate for guarding against the increased danger of acidosis in such conditions, and closely restricted fat to make up a total ration of 600 to 1,200 calories according to the individual case. This advice is contrary to the natural prejudice in favor of a high diet for repair of tissue or resistance to infection. But as a rule an increase of diet above the low figures mentioned belongs only to the final stage of recovery. The majority of the patients are overweight, and even in an exceptionally emaciated case these figures should be only slightly exceeded. There is little tendency to losing weight with the patient in bed, and it should be understood that several weeks of moderate undernutrition during the stage of infection and granulation creates by far the best condition for resistance and healing. It should be strongly emphasized that high diet plus high insulin dosage to control the sugar does not give equivalent results, and comparison of the two methods shows that an overfeeding program, especially with high allowances of fat, will needlessly sacrifice many lives.

As an incidental feature, we now at this Institute make the diet salt-free in gangrene cases. Many of these cases have more or less local swelling, and the reduction of this edema by salt exclusion distinctly improves the circulation. Some of the patients have more or less hypertension, and thus the salt-free diet is indicated. Hypothetically, the mere existence of arteriosclerosis may also be regarded as an indication. The salt restriction is subsidiary in importance as compared with the control of the sugar by diet. But we believe that it improves our results, though this impression could scarcely be supported by figures.

Besides diet, insulin is needed in the great majority of these cases, because quick and radical control of the sugar is of crucial importance. Also, the intoxication from the gangrenous area makes the sugar more difficult to reduce and intensifies the need for insulin, so that surprisingly large quan-

tities may be required temporarily in cases which, after cure of the gangrene, have excellent tolerance without insulin.

This toxic effect is often perceptible in cases with only a small black spot on a toe, without fever, malaise or any other suggestion of systemic reaction. It reaches an alarming point with sepsis and fever, when there may be difficulty in keeping the sugar normal even with dosage above a hundred units of insulin daily. The progress of the gangrene can almost be judged by the insulin requirement alone. Reduction of the required insulin indicates healing. On the other hand, a sharp rise of the insulin requirement is strongly significant of spreading gangrene and increasing intoxication. Sometimes when the condition appears satisfactory, with no visible enlargement of the gangrenous area and no fever or malaise, the blood sugar tests may show a rise which is barely controlled by increases of 10, 20 or more units of insulin. Unless some other cause can be discovered, it may be considered practically certain that the gangrene is spreading in the deeper tissues, and operation should be advised immediately instead of waiting for the graver manifestations which will surely appear soon.

As a general rule, with occasional exceptions, gangrene will heal under the medical treatment outlined if the necrosis or infection has involved only the superficial tissues. In other words, when the specific deficiency of tissue resistance is corrected by controlling the sugar, healing can be obtained in spite of poor circulation. Extensive deep infection or necrosis involving bones, joints or tendons will sometimes get well if there is an ample blood supply as indicated by strong pulsation in the dorsalis pedis or other vessels of the foot. With the usual advanced arteriosclerosis present, a small gangrene involving tendons or bone will heal in a minority of instances. Simple dry dressings usually suffice, or some mild wet dressing for pus. Atttempts to use antiseptics or even Dakin's solution may sometimes extend the necrosis. Electric light treatments, baking, or brief soaking in warm water may sometimes be beneficial but sometimes are distinctly harmful. Absolute rest of the foot is most important, the patient being kept either in bed or in a chair with the leg horizontal.

Surgical intervention is required nearly always when there is deep extensive gangrene or extremely poor circulation, and also in the majority of average cases where there is any necrosis of tendons or bone. The tendency nowadays is in the direction of surgical conservatism, but nevertheless it should not be forgotten that amputation at or above the knee is sometimes the most conservative procedure from the standpoint of saving life. There is not space to discuss the detailed indications, which need to be judged in each individual case by somebody with adequate experience.

By the best methods now available, patients with dangerous sepsis are frequently saved, though the mortality in such cases remains high. On the other hand, nearly all patients with simple gangrene can be saved, the exceptions consisting almost entirely of deaths due to the age or other general conditions independent of the diabetes.

The broad principle for the treatment of all local or general infections is to control the diabetes thoroughly and in addition use the same medical or surgical measures as in a non-diabetic. For carbuncle I favor conservative methods as opposed to radical excision. Tuberculosis remains one of the most serious complications, and it stands alone in requiring treatment with high caloric diets and frequently high insulin dosage to correspond. With this treatment the prognosis of the tuberculous diabetic is no longer hopeless as heretofore, but is fully as good as that of the non-diabetic with a similar infection.

New Diabetic Remedies

Attempts to administer insulin by mouth have yielded nothing of practical value. All other remedies tried or recommended in the past as having a specific influence on diabetes when taken orally must be classed as failures.

Recently attention has been attracted by the guanidine derivative, called synthalin, synthetized by Frank and collaborators in Minkowski's clinic at Breslau. The European reports leave no doubt that synthalin will reduce blood sugar in a manner somewhat like insulin. It may still be uncertain whether the benefit from such reduction of sugar is fully equivalent to the effect of insulin. At any rate, the toxicity of the new compound is such that it can be used as a substitute for insulin only in moderate quantities. The discoverers do not claim that it can entirely replace insulin in cases of any considerable severity. If it merely permits decreasing the number of insulin injections it will be a boon to many patients and a valuable advance in therapy, but its status must still be regarded as experimental.

The vegetable material called myrtillin was discovered by Richard I. Wagner in Vienna, and has been tested here experimentally and clinically. The entire laboratory investigation has been conducted by Wagner and he is entitled to the full credit in respect to both planning and execution. I have not been able personally to participate in this fundamental phase of the work or to check up its accuracy by any direct observations of my own; but since competent workers in other laboratories have reported confirmations in all details, it seems fair to assume that the findings are correct. If it be thus admitted that myrtillin can influence the assimilation of sugar in the normal organism and can produce benefits in partially and totally depancreatized dogs, there is a reason for making trials in clinical cases of diabetes. These trials have apparently shown beneficial effects in a number of patients, as well as negative results in a considerable number of others. Severe cases seldom give any indication of a favorable response to myrtillin, unless it be sometimes in the form of a diminished tendency to hypoglycemic attacks from insulin. The milder cases in older individuals offer the best chance of success, but unfortunately these are also the ones in which a positive demonstration of results is most difficult. Because of the well-known changes of tolerance which occur irregularly in the early stages of treatment, we have based our opinions chiefly upon the apparent results in a limited number of cases which had already been observed for

long periods under reasonably accurate conditions. These observations have been summarized in our earlier publications and will soon be published in detail. On the whole the experiences reported by other physicians who have tried myrtillin have been more favorable than our own, perhaps because they have dealt with a larger proportion of mild or otherwise suitable cases. At the same time a few of the best qualified judges, who have investigated myrtillin in the friendliest spirit, have obtained negative or unconvincing results—whether because of the refractory character of the cases in their series remains to be seen. It must be plainly recognized that the clinical tests do not afford a positive demonstration scientifically. If the animal experiments could be overthrown, it might be possible to discard all the clinical evidence as representing mere accident or coincidence. But if the influence of myrtillin upon experimental diabetes and upon the carbohydrate metabolism of normal animals and persons stands as scientifically established, there is some probability added to the view that the apparent clinical benefits are real and some burden of proof is placed upon anybody who would dismiss them as mere coincidence. Such a host of diabetic remedies have been enthusiastically recommended for a time and then been consigned to oblivion, that the utmost caution is necessary in affirming that anything has actual value; but on the other hand the worthless remedies have never been supported by valid animal experiments. We fully endorse the action of the A. M. A. Council on Pharmacy and Chemistry in withholding approval of myrtillin pending fuller investigation, because the widespread exploitation of a useless medicament would be a misfortune. It is at least beyond question that myrtillin is harmless, and the mere swallowing of a tablet three times a day is not even an inconvenience to the patient. The investigation of the material in a number of selected clinics therefore seems to be the right procedure at this stage. It should be made clear in advance that myrtillin is not insulin or a powerful substitute for insulin; that its action if real is not spectacular and will not revolutionize the general methods or results of diabetic treatment.

The world-wide movement in the direction of oral medication seems to represent the chief tendency in recent diabetic research. From the scientific standpoint insulin is the specific and ideal remedy. But the weighed diet and the hypodermic injections are irksome to patients, and human nature itself must furnish much of the explanation why the ideal diabetic remedy has thus far made no perceptible change in mortality figures. If anything can be found which will offer a more convenient and agreeable way of controlling diabetes, it will probably be an aid to some extent in reducing the death rate.

In conclusion, it is theoretically possible to enable diabetic patients to live as long and almost as efficiently as if they had never had diabetes, provided treatment is begun at a reasonable time and is carried out with reasonable thoroughness. It is the task of the medical profession to accomplish the practical realization of this ideal so as to reduce the present high mortality from this disease.

The Occurrence of Anemia in Myxedema*†

By Charles T. Stone, B.A., M.D., F.A.C.P., *Galveston, Texas*

When William Gull, in 1873, first described the disease which Ord, in 1877, designated Myxedema, a clinical picture so comprehensive as to scope and accurate in detail was given to the profession that little was left for subsequent generations to add. Murray's successful treatment of a patient with the disease by the subcutaneous injection of a glycerine extract of thyroid gland, in 1891, so completed the knowledge upon the subject that nothing of value was added, excepting the oral administration of thyroid substance, until in 1893 it was shown by Magnus-Levy that there is great and constant lowering of the basal metabolic rate. Thus there was constructed a clinical knowledge of myxedema by which physicians have come to recognize it as a definite though relatively uncommon cause of disability.

From the clinical point of view the recognition of typical examples of myxedema is comparatively easy, but from time to time cases are encountered in which the more characteristic symptoms and signs are not so manifest, and in which the real nature of the illness is obscure. In such instances the dominant finding is frequently a severe or moderately severe anemia which may be erroneously interpreted as the cause rather than the result of the illness. There are now fairly numerous clinical reports of cases of myxedema in which an anemia was the most conspicuous feature, as for example those of MacKenzie (1), Janney and Engel (2), Baker (3), Warfield and Greene (4), Minot (5), Emery (6), and others. Strangely enough in many of the reported cases with marked anemia the more common and readily recognizable symptoms of myxedema were inconspicuous.

Experimental Studies

From the experimental side there is evidence in support of the belief that marked reduction in the function of the thyroid gland is often followed by a depression of the erythropoiesis in the bone-marrow. Esser (7) has reported the results of his studies upon dogs and rabbits subjected to total thyroidectomy. Following the operation the animals showed a progressive lowering of the number of red blood cells and the percentage of hemoglobin. Experimental studies by Kishi

*From the Department of Internal Medicine, University of Texas, Medical School, Galveston.

†Read before the American College of Physicians, New Orleans Clinical Week, March 6, 1928.

(8) and Mansfield (9) produced similar findings, and brought out the additional facts that in the experimentally produced anemias of animals blood regeneration was delayed by thyroidectomy, and that thyroid feeding in normal animals might bring about an increase in red cells and hemoglobin. These experiments were reported between 1904 and 1907, but they appear to have been carefully controlled, and doubtless, the conclusions drawn are well founded. Some difficulty in the interpretation of the results is, at times, occasioned by reason of the fact that some of the animals developed tetany, evidently because of removal of the parathyroids with the thyroid. However, disregarding the instances in which this occurred, the uncomplicated experiments justify the conclusion that anemia may follow a deprivation of the thyroid secretion. The experimental anemia so produced is usually of the secondary type, without the presence of abnormal red cells or striking alteration of the leucocyte and differential counts.

Clinical Myxedema and Anemia

In order to arrive at some idea as to the incidence of and the facts relative to anemia associated with clinical myxedema the records of all patients with the disease seen in office and hospital practice over the period of the past eight years were reviewed. In twenty-three instances was the information sufficient to permit a detailed study. The blood counts, basal metabolic rates, results of treatment (in some instances) and other essential data are shown in Table I.

The outstanding facts in this group of twenty-three patients are as follows. All but one were of the white race. Nineteen, or 82.6 per cent, were females, and four, or 17.4 per cent, were males. The average age at the time of observation was 42.7 years; the youngest and oldest patients were 21 and 53 years of age respectively. Basal metabolic rates (22 cases) averaged 30.5 per cent with extremes of minus 17 per cent and minus 45 per cent. A striking observation was a complete lack of parallelism between the basal metabolic rates and the blood counts, although in all four patients with rates of minus 40 per cent or more, some degree of anemia was present. Thirteen patients, or 56.5 per cent of the series, showed a reduction in the number of red blood cells and in the percentage of hemoglobin. The lowest erythrocyte count was 2,750,000, and the highest 5,820,000, with hemoglobin values of 40 per cent and 113 per cent as the extreme variations. The majority of the patients in whom anemia was present showed only a slight or moderately severe change, and in most instances the anemia was of the secondary type. The color index was found to be above 1.0 in five cases, the highest being 1.2. Abnormal red cells were reported but once, and then only anisocytosis and poikilocytosis were observed. In every case, excepting one, the leucocyte and differential counts were within normal limits, presenting no feature characteristic or diagnostic of myxedema. Five cases had follow-up blood counts made after the basal metabolic rate had been elevated by treatment and in each it was found that the cells and hemo-

globin had been caused to approach the normal values.

Three patients of the series (Case numbers 5, 15, and 18) presented an anemia as a salient finding and had been treated for anemia elsewhere—two for pernicious anemia (cases 5 and 15) and one (case 18) for secondary anemia—for periods varying from three to nine years. The case histories of these three patients are herewith detailed.

Case Reports

Case No. 5. Mrs. A. U., aged 50, a housewife, was first seen September 13, 1922, complaining chiefly of weakness. Except for the death of her mother from cancer, the family history was unimportant. She had always been very healthy, having been confined to her bed only at the birth of her children, and following an operation for repair of a lacerated cervix. A little more than three years previously she noticed weakness, a curious empty feeling in the head and dizziness. In time all of her symptoms became so pronounced that she could no longer perform her usual household duties. A physician found an anemia, which was thought to be of the pernicious anemia type, and she was given iron and arsenic, which she took intermittently for the past two years. She thought the arsenic caused swelling of the face and ankles. All of her teeth were extracted four months before she came under observation.

The patient appeared quite pale, and there was a distinct yellowish tint to the skin. Slight non-pitting edema of the face and extremities was present. The mucous membranes were pallid. The blood pressure was 110 systolic and 70 diastolic. The pulse was 68; the temperature 97.6 F; weight 132; calculated ideal weight 150. The blood count was: red cells, 3,030,000; hemoglobin, 70%; color index, 1.2. The white and differential counts were normal (Table I, case 5), and abnormal red cells were not found. The Wassermann was negative. The urine was normal. The gastric contents showed: free HCL 37, total acidity 45, mucus and occult blood were absent. The basal metabolic rate was minus 35 per cent. After the administration of thyroxin 1.8 mg. daily for a year the basal metabolic rate was minus 5, and all symptoms were relieved. Her blood count was: red cells, 4,300,000; hemoglobin, 81%; color index 0.9. A continuation of treatment maintained her health at normal.

Case No. 18 (Table I). Miss B. H., aged 50, who had a good family and personal history, began seven years before to complain of indigestion, which consisted of bloating, with gas and constipation. For relief of these symptoms the appendix was removed, but she was not benefitted. Later on she developed a bad taste in the mouth, weakness, and giddiness. A blood count showed an anemia, for which she took iron pills by mouth and sodium cacodylate by injection. This treatment she continued most of the time for the preceding five or six years. Many abscessed teeth were extracted. In spite of these measures she lost ground steadily, and became so weak that she spent much of her time in bed. When she was first seen

TABLE I. THE BLOOD IN TWENTY-THREE CASES OF MYXEDEMA

Case No.	Initials	Race	Sex	Age	Date	Basal Metabolic Rate	Red Blood Cells	Hemoglobin	Index Color	White Cells	Neutrophils	Lymphocytes	Large Mononuclear	Transitionals	Eosinophils	Basophils	Abnormal Red Cells
1	N.N.	W	F	46	5-31-21	—40	3,140,000	40	0.6	7,300	69	31					Anisocytosis
																	Poikilocytosis
2	T.H.B.	W	F	37	11-12-20	?	4,130,000	74	0.9	8,400	62	31	3	2	2		None
3	A.B.	W	F	39	2-23-22	—23	3,008,000	70	1.2	6,400	70	26	4				None
4	B.K.	W	M	21	5-11-22	—30	3,650,000	73	1.0	6,200	50	44	2	3	1		None
5	A.U.	W	F	50	9-15-22	—35	3,030,000	70	1.2	7,200	58	36	1	3	2		None
					1- 9-23	— 4	4,300,000	81	0.9								
6	F.P.H.	W	M	48	7- 7-23	—30	5,820,000	113	0.9	8,200	65	30	1	3		1	None
7	S.H.M.	W	F	53	7-12-23	—17	3,700,000	70	0.9	6,200	58	34	4	3	1		None
8	N.B.	W	F	27	9-15-23	—36	4,592,000	80	0.9	5,960	67	27	4	1	1		None
					6-10-24	+16	4,910,000	81	0.9	6,000	65	32	2	1			None
9	F.S.	W	M	24	9-30-24	—36	5,380,000	95	0.9	8,000	61	28	7	3	1		None
10	N.R.	W	F	37	12-31-24	—31	4,840,000	96	1.0	8,400	56	38		5	1		None
11	J.V.J.	W	F	37	2-25-25	—20	4,576,000	75	0.8	9,400	73	25	2				None
12	M.K.	W	F	58	5-25-25	—27	5,600,000	98	0.9	6,200	72	26		2			None
13	C.A.E.	W	F	34	8- 2-27	—34	3,600,000	75	1.0	4,900	79	20		1			None
					2-21-28	+ 3	4,230,000	82	0.9	7,100	63	33		2	1	1	None
14	R.B.	W	F	52	7- 6-27	—25	2,750,000	50	0.9	2,000	73	20	4	2	1		None
15	G.W.	W	M	53	8-19-27	—45	3,130,000	55	0.9	9,600	50	47	2	1			None
					1-21-28	— 7	4,310,000	80	0.9	8,800	52	43	2		3		None
16	W.A.V.	W	F	51	11-23-27	—23	3,300,000	78	1.2	6,100	64	19	8	4	2	3	None
17	W.A.H.	W	F	53	6-23-27	—41	3,950,000	85	1.1	6,750	65	33		2			None
18	B.H.	W	F	50	7-19-27	—40	3,580,000	68	1.0	6,800	50	48			2		None
					10-17-27	+ 5	4,200,000	81	0.9								
19	A.L.	W	F	45	11- 1-27	—24	3,660,000	71	1.0	6,200	59	37	2	2			None
20	E.F.S.	W	F	34	11-22-27	—28	4,000,000	75	0.9	6,200	56	41	2		1		None
21	A.B.	W	F	46	12- 9-27	—39	4,375,000	73	0.8	5,050	75	16	4		5		None
22	N.S.	N	F	46	1-16-28	—20	4,600,000	65	0.7								
23	L.H.	W	F	41	2-21-28	—27	3,450,000	75	1.1	7,950	54	32	10	2	2		None

July 19, 1927, the skin was dry, pale, and had a yellowish waxen look. Chronic follicular tonsilitis was present. The abdomen was considerably relaxed and was of the ptotic type. The heart rate was 60; the rhythm was normal. Blood pressure, systolic 104, diastolic 70. The temperature was 99 F; weight 135 pounds; calculated ideal weight 144 pounds. Urinalysis and Wassermann were negative. The blood count was: red cells, 3,580,000; hemogobin, 68%; color index, 0.9; leucocytes and differential count, normal. Gastric analysis, free HCL 0, and a total acidity that varied between 5 and 16. The basal metabolic rate was minus 40%.

Her treatment consisted of dessicated thyroid nine grains daily, and dilute hydrochloric acid minims twenty, and pepsin grains twenty after meals. After a few months of treatment her gastro-intestinal symptoms and weakness were greatly improved. October 17, 1927, the basal metabolic rate was plus 5. January 31, 1928, the blood count was: red cells, 4,220,000; hemoglobin 81%; color index, 0.9.

Case 15. G. W., a farmer, aged 53, was admitted to the John Sealy Hospital August 19, 1927, complaining of weakness, and swelling of the body. His father died at 52 of gastric cancer; and one sister had a goiter of unknown type. In the past his only illness of consequence was typhoid fever at 30 years of age. This left him with a chronic cholecystitis, which was drained surgically five years ago. The present illness actually began in 1919 when he had diarrhea, passing four or five thin offensive stools daily. At that time he was a patient in the John Sealy Hospital, where a diagnosis of pernicious anemia was made. On June 25, 1919, the blood count was: red cells, 2,790,000; hemoglobin, 78%; color index, 1.5; white cells, 4,800; neutrophiles, 46%; lymphocytes, 49%; large mononuclears, 3%; transitionals, 1%; eosinophiles, 1%. The urine and Wassermann were negative. Achylia gastrica was present. He received during the summer of 1919, three blood transfusions totaling 2500 cc. Considerable improvement was made in his blood count, which rose after the transfusions to: red cells, 4,280,000; hemoglobin, 90%; white and differential counts normal. However, he was greatly improved in health, but was unable to work. In 1926 he consulted a physician, in a neighboring city, who gave him another transfusion, but with only slight benefit. At the time of his last admission to the hospital, August 19, 1927, his complaint was weakness, abdominal discomfort and the passage of three or four loose stools per day.

The patient showed marked pallor of the skin and mucous membranes. The skin was dry and edematous. Over the legs the edema pitted on pressure, but did not do so over the rest of the body. The weight was 179 pounds; calculated ideal weight 178. During his stay in the hospital the temperature varied between 97 F and 100 F; and the pulse between 80 and 100. The blood pressure was: systolic, 102; diastolic, 85. The blood count showed: red cells, 3,130,000; hemoglobin, 55%; color index, 0.9; white cells, 9,600; neutrophiles, 50%;

lymphocytes, 47%, large mononuclears, 2%; transitionals, 1%. Abnormal red cells were not observed. The urine was negative, and other evidences of renal impairment were lacking. Achylia gastrica was present. By the teleoroentgenogram, August 26, 1927, the transverse diameter of the heart at the apex was 16½ cm; the aortic arch 7 cm; transverse inside diameter of the chest 28 cm, which was an increase above normal of 5 cm. in the cardiac measurement at the apex. The basal metabolic rate was minus 45%. Under full doses of dessicated thyroid his weight dropped to 150 pounds in twenty-one days, a loss of 29 pounds, which was due very largely to the removal of the edema. On October 19, 1927, less than two months after the treatment was begun, the teleoroentgenogram showed: transverse diameter of the heart at the apex was 11 cm.; aortic arch 6 cm.; transverse inside diameter of chest 28 cm., a loss in width of the heart of 5½ cm., or a size that was within normal limits. The last observation of the patient on January 21, 1928, showed that his basal metabolic rate was minus 7%. The blood count was: red cells 4,310,000; hemoglobin, 80%; color index, 0.9; white and differential counts, normal. The weight was 126 pounds. Symptomatically he was relieved, and felt strong enough to walk four or five miles daily.

Comment

The statement made in 1881 by Charcot (10), who is credited with being the first to observe that patients with myxedema might be "anemic to a high degree," is fully justified by the findings in this series of myxedema patients. Of especial interest are those myxedematous subjects who show a combination of anemia and achylia gastrica, because of the possibility of confusing the diagnosis with pernicious anemia. The normal leucocyte and differential blood counts, together with an absence of abnormal red cells should serve to put one on guard.

In the present series of twenty-three cases of myxedema, achylia was found in four, or 25%, of sixteen cases in which the gastric contents were examined. The exact relationship between the hypothyroidism and the achylia is uncertain, but the fact that there has been a persistence of the achylia in all re-examined cases indicates perhaps that they are coincidental. Lisser (11), and others have reported the presence of both myxedema and pernicious anemia in the same individual, a possibility which should always be borne in mind. In very doubtful cases the effect of treatment may be necessary to complete the differential diagnosis. However, in the large majority of instances it is true that the anemia found in connection with clinical myxedema is due to the lowered thyroid function, and it is relieved by the administration of thyroid substance. It is generally found in myxedema anemia that the blood count does not show such a high grade anemia as the physical appearance of the patient suggests, which is doubtless due to the peculiar characteristics of the skin in myxedema.

The manner in which the anemia secondary to myxedema is produced seemed best explained on the basis

that there is a depression of function in the hematopoietic system by the hypothyroidism. This view is consistent with the belief that there is a diminished function of other tissues, and obviates the necessity of presuming that the thyroid gland elaborates a special hematopoietic hormone, as some have suggested.

Conclusions

1. The blood findings in a series of twenty-three cases of myxedema have been presented.

2. In this series a secondary anemia occurred in 13 of the cases.

4. The anemia is due to the lowered content of thyroxin in the body acting upon the blood forming organs.

5. The blood changes in myxedema are concerned almost exclusively with the red blood cells and hemoglobin.

6. The leucocytes are usually normal in number, and the differential counts are inconsequential.

7. The administration of thyroid substances usually causes the anemia to disappear, while other treatment fails until the specific deficiency is corrected.

3. The similarity of hypothyroid anemia and pernicious anemia has been discussed.

REFERENCES

(1) MacKenzie, George M.: Anemia in Hypothyroidism, J. A. M. A., 86: 462, Feb. 13, 1926.

(2) Janny, N. W., and Engel, H. E.: Concerning the Diagnosis and Treatment of Hypothyroidism, Arch. Int. Med., 26: 297, Sept. 1920.

(3) Baker, W. A.: Dysthyroidism, a Factor in Secondary Anemia, J. Kansas M. Soc. 24: 321, Nov., 1924.

(4) Warfield, L. M., and Greene, I. W.: Hypothyroidism and Its Relationship to Chlorotic Anemia, J. Michigan M. Soc. 24: 79, Feb., 1925.

(5) Minot, George R.: Myxedema with Anemia, M. Clin. N. Amer., 4: 1743, May, 1921.

(6) Emery, E. S., Jr.: The Blood in Myxedema, Am. J. M. Sc., 165: 577, April, 1923.

(7) Esser: Blood and Bone Marrow Following Failure of Thyroid Function, Deutsches Arch. f. klin. Med., 89: 576, 1907.

(8) Kishi, K.: Contributions on the Physiology of the Thyroid Gland, Virchows Arch. f. path. Anat., 176: 260, 1904.

(9) Mansfeld, G.: The Blood Picture and the Thyroid Gland, Magyar Orvosi Archivum, 13: 188, 1912.

(10) Charcot: Quoted by Emery, see footnote 6.

(11) Lisser, H.: Bedside Diagnosis, Blumer, G.: W. B. Saunders Co., Phila., 1928.

Editorial

JOHN HUNTER'S VIEWS ON CANCER

Hunter's conceptions of "cancer" are condensed within about a dozen pages in his Lectures on the Principles of Surgery. Nevertheless, within this small space are contained statements of facts that hold good today. This is particularly true of his views on the treatment and cure of cancer. The accuracy of his judgment is astonishing when we consider that it is based wholly upon the natural-history method of observation and deduction. That is, *all* that he knew of cancer was wholly clinical and from his clinical experiences he drew his conclusions. It was as if he mentally arranged his cases on a museum shelf, noting, comparing, classifying and cataloguing, and finally making his deductions. Of the cellular and histologic nature of cancer he, of course, had not the slightest conception. Of what lay behind the gross appearances he possessed very little knowledge, and his interpretations of what he saw when he cut into a cancer were purely hypothetical and for the most part incorrect, when viewed from the standpoint of modern pathology. There could, of course, be no exact science of Gross Pathology until gross morphology had a solid foundation of Cellular Pathology. But without this solid foundation Hunter probably went as far as it was possible for the human mind to go in mere clinical observation and deduction. The conditions grouped by Hunter under the term cancer comprised many things of non-neoplastic nature, just as still happens in the case of purely clinical diagnoses of today, but naturally more frequently in Hunter's time. He, himself, recognized this. He says of cancer:—"The diseases most commonly classed under this name are in appearance very different and probably are very different in their nature; they should not, therefore, be called by the same name. I would call that cancer which produces the following effects: viz., a circumscribed tumefaction with much hardness, and a drawing-in of the skin over it, as if the cellular membrane underneath were destroyed; then a species of suppuration takes place in the center, and ulceration of the external surface. This is its most frequent appearance." How true is this description of the most common aspects of superficial carcinoma—the destructive infiltration and induration, the umbilication or retraction, and the central necrosis and ulceration! We are quite sure that Hunter made few mistakes in his clinical diagnoses of carcinoma when he applied such criteria as these. As to the location, he then goes on to say: "It most frequently attacks the conglomerate glands, and first the female breast; also the uterus, the lips, the external

nose, the pancreas, and the pylorus; besides which the testicle is very subject to it, though that is not to be classed among the conglomerate glands. So that when I speak of cancer, I mean a peculiar disease in some of the above parts." As to the frequency of location in the organs enumerated we would still agree, with two exceptions, the pancreas and testicle. As Hunter mentions the pylorus after the pancreas it is very possible that he bases his opinion of pancreatic cancer on advanced stages of primary gastric cancer involving the pancreas. Such a secondary involvement of the pancreas is common enough in the late stages of pyloric cancer, and Hunter saw only late cases at autopsy. His inclusion of the testis in the list of the frequent sites of cancer is puzzling. Destructive diseases of the testis must have been more common in his time than in ours; and it is most probable that tuberculosis, gumma and suppurative infections of the organ made up the bulk of the testicular diseases regarded by him as cancer. Particularly in the case of tuberculosis of the testis involving the scrotum would his description of the external appearances apply. After his definition and mention of the most frequent sites of cancer he then goes on to enlarge upon the peculiar characteristics of cancer and to give its differential diagnosis from scrofula. "When small they probably cannot be distinguished; but as they increase, the distinction is more easy. If cancer, it will vary in appearance by becoming less circumscribed, not having so determined an outline, from the cellular membrane about it becoming diseased; the skin will be less movable, the nipple more or less retracted, and the lymphatic glands going to the axilla will swell." What a concise and perfect description of the most important clinical differential facts this is! He then after giving the characteristics of scrofula goes on to say: "In cancer, the surrounding parts that are affected by continued sympathy also become cancerous near the skin, that is, all the parts become blended in one mass; but in scrofula, although the surrounding parts are in action, yet that action is not so scrofulous as the part itself; so that the skin will sometimes heal over the scrofulous tumor, as I have seen in the testicles when suppuration had taken place, by which I determined the disease was not cancerous. . . . . Cancer is one of the first class of our first division of poisons, viz., that which only produces local effects, though it has been supposed to contaminate the constitution, which would be terrible indeed, as we have no specific nor even a palliative for it. . . . . When a cancerous tumor has been removed often, the sore does not heal, or breaks out again. Sometimes it breaks out in another part of the body, which has been thought a proof of its arising from the constitution. This last circumstance as often arises where there has been one; it does not, therefore, depend on that circumstance as a cause. However, the operation having or not having been performed does not affect their argument, unless they could prove that cancer is an act of the constitution, and acts as a chain or concentration of the cancerous poison, and that by stopping this it must go some-

where else. But the proportion of those who have it break out in two different parts of the body, compared with those who have it only in one, is about half what the latter bear to those who have not the disease at all, or about five hundred to one. I never saw it in two different parts of the same person, but I have seen it in more than two distinct points of the same part. It often arises in distinct points of the same breast, but seldom at the same period; and some of these may be so much in their infancy when the operation is performed as not to be observable, but afterwards increase and require a second operation. . . . . It is, therefore, best to extirpate the breast completely at once, to remove the whole complaint. . . . . A scirrhus or cancer appears to have three modes of contaminating: 1st, by continued sympathy, which is common to other diseases; 2ndly, by remote sympathy, which is peculiar to itself; 3rdly, by contact, or communication of its matter to other parts by contamination. I have called these consequent cancers, in opposition to the original." How much one would like to be able to explain to John Hunter's shade, if one should ever meet it in etherial wanderings, the knowledge we today possess of metastasis. In reading John Hunter we meet with passages such as this when we can almost painfully feel the puzzled gropings and effort of his mind in the attempt to understand phenomena, which, at that stage of the development of human knowledge, could not be understood at all. Hunter is fully convinced that cancer is a local disease, and he goes on to argue this point. He asks: "Does cancer then produce any effect on the constitution? When it has existed a long time we find slight fever and hectic; but this is no more than the effect of all long-continued irritations, or sores which are not disposed to heal, but no peculiar effect is produced on the constitution." This is no more than the modern serological laboratory has been able to say. "It has been said that cancers are produced by ill health as rheumatisms are; but this arises from the age of cancer being the age of such complaints, and being thus the predisposing cause of both, but not particularly of the cancerous disposition."

Hunter then compares the cure of cancer with that of venereal infection, concluding, as follows:—"If we remove a cancer and no absorption will take place, the sore will heal and the constitution will not suffer, but then the ***whole*** must be removed. . . . . Otherwise it will return. . . . . If removed and there has been absorption, the parts heal, though the consequent [*secondary*] cancer goes on; but if the whole cancerous parts are removed, the constitution is free. . . . . This shows that a cure is the consequence of a total removal of the parts, notwithstanding absorption has taken place, if all the diseased parts are removed." Such statements of fact are precisely the battle-cry of the propagandists for cancer-prevention of today. "The only powers of contamination of this poison [cancer] are: 1st, When it spreads from the center, thus producing a disposition to the disease in the surrounding parts, and an extravasation of interstitial matter; 2ndly, when the disease extends to dis-

tant parts, as when little tumors form under the sin at some distance, not in the line of absorbents; and 3rdly, when it produces the same disease in the absorbents and glands." The rate of growth of cancer is then described by Hunter, sometimes slow, sometimes rapid, sometimes accelerated by inflammation, operation, etc., but in general he regards the growth of cancer as slow and, therefore, the more dangerous. As to the cause of cancer, he considers the three predisposing causes to be: "Age, parts and hereditary disposition; perhaps climate also has considerable effect, though not a predisposing cause. The cancerous age is from forty to sixty years in both sexes, though it may occur sooner or later in certain cases. The testicle, for instance, often becomes cancerous at twenty or thirty; but then not from the disposition of the parts alone, but from accident." As we can hardly believe that malignant teratoma of the testis was more common in Hunter's time than it is today, it is evident that the more frequent destructive disease of the testis in the young men of his time was either tuberculosis, or venereal disease. "Cancer has been supposed to be in young people's eyes [so-called malignant glioma, sarcoma or retinoblastoma]; therefore, it is most probable that the breast is less subject to it at this age, and other parts are not so much confined to age in this disease. We often see tumors in the breast at thirty, and probably some of them are cancerous, although scrofula is more to be suspected. When cancer occurs in the breast of women under forty, it is *more rapid in its progress than when the patient is older, and also more extensive* [confirmed in our time], so that the operation succeeds better in the latter on this account. However, we seldom find it in the very young or very old. Although of the two it is most frequent in the latter. When it occurs in the young, does it not show a very strong disposition for this disease, and, therefore, more danger, from a greater likelihood of its returning." Hunter next discusses more in detail *"the parts most disposed to cancer* [his own italics], those peculiar to the sexes, as the breasts and uterus in women and the testicles [!] in men. Cancers are more frequent in women than in men, in the proportion of three to two; owing, perhaps, to the more frequent changes taking place in these parts in the former. It is that change which renders them unfit for conception and changes the whole system, which is particularly obnoxious. Thus, the three predisposing causes are: 1st., a peculiar part; 2ndly, the age of the patient, and 3rdly, the peculiarities of the part at this age. The parts next in order of frequency, and which are common to both sexes, are the conglomerate glands about the lips, nose, throat, tongue, pancreas, stomach, especially the pylorus; intestines, especially the rectum. Besides these, we have it in the eyes and glans penis. The disease also appears in other parts of the body; but, as most other parts are similar in structure it does not attack one more than another. It sometimes falls on the bones from contamination, but on no one in particular." In his next paragraph, which is headed *"Whether Hereditary,"* he

goes on to say: "Some suppose cancers to be hereditary; but this I can only admit according to my principles of hereditary right; that is, supposing a person to possess a strong disposition or susceptibility for a particular disease, the children may also, but I have not yet ascertained the generality of this fact. In many persons it would appear that some of the predisposing causes are sufficient to become the immediate ones; as when the diseased action takes place at a certain stated time, without any immediate cause." Could there be any more concise statement of the modern belief in the heredity of cancer susceptibility or predisposition, and its relationship to extrinsic causes! As to the effect of climate upon cancer, Hunter had only heard that they are very rare in the West Indies, and apparently not frequent in the Friendly Isles, in spite of the fighting contests held between women in which the breast is the chief point of attack; he, therefore, on the basis of such information thinks it is most probable that climate has some power, both in disposing to the disease and in preventing it. Following the discussion of the predisposing causes, Hunter describes the symptoms of cancer in detail; the majority of his statements made in regard to these are still accepted at the present time. He saw no local symptoms peculiar to cancer; they are only such as would arise from any injury to the part involved capable of producing the same degree of local injury, irritation and pain, which will vary in character and degree with the nature of the part involved, as, in the bladder, the symptoms wiill resemble those of stone; in the rectum, purging and tenesmus; in the stomach, sickness and vomiting; within the skull, headache and coma. Cancer, he believed, "gives rise to no constitutional symptoms, except such as would arise in other diseases from the long continued wearing pain and perpetual discharge." Finally, as to his views as to treatment; here again his marked modernity shows itself. How far removed from quackery was John Hunter in all of his conceptions of treatment! This is the most remarkable thing about him, considering the age of quackery in which he lived. He would be modern even today, as far as the treatment of cancer is concerned, and no doubt would have raged violently and hotly denounced the cancer-cures of today, as he did that of Mr. Plunkett, in his own day. Speaking of arsenic as a cancer cure, he says: "Arsenic seems to have some power of this kind [curative] and its effects might be increased, by being used internally and externally; but its use is very dangerous, and I am afraid insufficient for the disease. This is a remedy which enters into the empirical nostrums which are in vogue for curing cancer; and among which Plunkett's holds the highest rank. But this is no new discovery, for Sennertus, who lived the Lord knows how long ago, mentions a Roderiguez and Flusius, who obtained considerable fame and fortune by such a composition. I was desired to meet Mr. Plunkett, to decide on the propriety of using his medicine in a particular case! I have no objection to meeting anyone; it was the young

one; the old one is dead, and might have died himself of a cancer for aught I know. I asked him what he intended to do with his medicine. He said, 'To cure the patient.' 'Let me know what you mean by that; do you mean to alter the diseased state of the parts?, or do you mean by your medicine to remove the parts diseased?' 'I mean to destroy them', he replied. 'Well then, that is nothing more than I or any other surgeon can do with less pain to the patient.' Poor Woollett the engraver died under one of these cancer-cures: he was under my care when this person took him in hand. He had been a life-guards man, I think, and had got a never-failing receipt. I continued to call on Woollett as a friend, and received great accounts of the good effects; upon hearing which, I said if the man would give me leave to watch regularly the appearance of the cancer, and see myself the good effects, and should be satisfied of its curing only that cancer (mind, not by destroying it) I would exert all my power to make him the richest man in the kingdom. But he would have nothing to do with me, and tortured poor Woollett for some time; till at last I heard the sound testicle was gone, and at length he died." Hunter sums up his views on the cure of cancer in the following:—"No cure has yet been found; for what I call *a cure is an alteration of the disposition and the effect of that disposition* [*editor's italics*], *and not the destruction of the cancerous parts.* But as we have no such medicine, we are often obliged to remove cancerous parts; which extirpation will often cure as well as we could by changing the disposition and action." Hunter then, for several pages, gives the technical details of the treatment of cancer, and every young surgeon should know these several pages by heart, and apply in his own work the knowledge of operation, recurrence and metastasis, re-operation, etc., that he will find there. He will profit much. On reading Hunter one's admiration and wonder grows by leaps and bounds. What a wonderful man—but not an agreeable one! But what a mind! What a pity Hunter came so soon; if he belonged to us, today, and did for modern medicine, based upon cellular pathology, what he did for the medicine of the 18th Century, where might our science not be advanced—to what heights? Even his unpleasant, rough, fighting, smashing honesty is needed today—we still have cancer-cure quackery to be treated as he disposed of Mr. Plunkett, but we have become too gentle, or afraid—which!

Abstracts

The Influence of Environment on Rheumatic Infection in Childhood. By REGINALD MILLER (The Lancet, May 19, 1928, p. 1005).

Is there any evidence that environment plays an important part in the production of juvenile rheumatism? Considered as a widespread endemic disease of England, juvenile rheumatism shows one outstanding feature. Namely, it is massed amongst the children of the poor, and practically absent from the children of the well-to-do. This class incidence is so clear that it is evident that we cannot hope to understand the large scale production of the disease until we know the explanation of it. Have we any direct evidence that the environment is the correct explanation of this class incidence. The Medical Council's Report into the incidence of rheumatism in poor-law residential schools offers conclusive evidence in this line. Four schools, housing about 1800 children, who all came from the poorer classes, were examined over a number of years. Left in their own homes it is impossible not to suppose that dozens of instances of rheumatism would have arisen amongst them; yet transferred to the residential schools they remain practically free of the infection. On this single piece of evidence alone we may confidently base the opinion that juvenile rheumatism is essentially an environmental disease. There are, of course, many other confirmatory proofs of this view. There are other possible explanations of the freedom from rheumatism enjoyed by the children of the richer classes, such as contagion, heredity, and diathesis. As to the two last named factors the evidence shows that they cannot be of great importance. The theory of contagion has no sort of support among clinical workers on the rheumatic problem. Further, spread by contagion will not explain the class incidence of the disease, and is not in agreement with the modern bacteriological conception of rheumatic infection. If the last is true rheumatism must be grouped with such infections as appendicitis and lobar pneumonia, rather than with diseases due to imported organisms such as tuberculosis. Family cases of appendicitis and pneumonia occur synchronously or in close succession, but no one thinks that contagion accounts for the thousands of these cases that occur. To sum up, therefore, the general question of the influence of environment on juvenile rheumatism, we may regard this influence as so powerful that it is fair to regard the rheumatism of childhood as an environmental disease. This view is supported by the general trend of medical opinion in England. What are the environmental factors of importance in the production of juvenile rheumatism. Climatic and seasonal incidence show that a combination of damp and cold predisposes to the disease. Although poverty is a predisposing cause of immense importance, it is not merely poverty per se that is responsible, since the very poorest class shows a lower incidence than the class of the upper poor; the disease hits particularly the families of policemen, postmen, railwaymen and decent artisans. No other disease but dental caries shows quite the same class incidence as rheumatism. Rheumatism is a disease of city life rather than of rural, and of industrial towns rather than of residential towns. The part played by diet and general nutrition is not clear. Miller believes that damp dwellings play a very important part in the predisposition of children to the disease. Rheumatism maps show that the greatest number of cases come, not from the poorest streets, but from those close to canals and submerged streams. The middle floors of houses, which are as a rule the driest, provide the fewest cases. The relationship to poverty is apparently

chiefly a relationship to residence in damp dwellings. The greatest incidence of rheumatism is to be found among the poor who live in damp areas and in damp houses. Miller concludes that juvenile rheumatism must be regarded as an environmental disease. General lowering of the resistance is produced by such factors as poverty, urbanization and industrialization; the tendency to rheumatic infection is largely determined by living in damp rooms, exposure to wettings, chills, catarrhs, etc. Poverty and damp houses are two chief environmental factors. Altering the environment of children is sufficient to prevent the appearance of the infection amongst them.

Acute Rheumatism in Childhood. *By* C. J. McSweeney (The Lancet, May 12, 1928, p. 959).

The study of rheumatism occurring in the school-children of Cardiff, made by the Health Officers of that city in 1927, comes to somewhat different conclusions from those in the preceding abstract of Miller's study of the disease in London children. In Cardiff 214 rheumatic children were studied; 65 of these had rheumatic fever, 133 had rheumatic pains at some time or other, 129 had rheumatic carditis resulting in permanent valvular disease, 44 had rheumatic carditis which at the time of examination had not yet produced permanent valvular disease, 9 cases showed erythema nodosum and 7 cases showed arthritis. The summary of findings obtained by this study was as follows: No significant differences as to size of tonsils or frequency of sore-throats were found to exist when a series of observations on rheumatic children was compared with a series of observations on a similar group of non-rheumatic children. Chorea, permanent heart disease and other rheumatic manifestations were found to have developed in several cases after tonsillectomy had been performed. During the inquiry some slight evidence of the infectivity of rheumatism was found. Overcrowding did not seem to predispose to the onset of rheumatism, but 13 of the 14 rheumatic children found living under over-crowded conditions showed evidence of cardiac involvement. The incidence of dampness in the houses of 201 rheumatic children was not significantly higher than in the houses of 108 non-rheumatic children. Ground-floor dampness was found to exist more frequently in the houses of rheumatics (which were, as a rule, older houses) than in those occupied by the controls but this did not seem to produce a tendency towards any particular type of rheumatic onset. A general dampness of the house was more often associated with the onset of rheumatic pains than other types of onset, but the differences were not significant. Dampness of houses, of whatever distribution, did not appear to predispose to the onset of chorea in preference to any type of onset. Living in damp houses did not predispose especially to rheumatic fever or to cardiac involvement. No close relation was found to exist between proximity to water and the development of rheumatism. (These Cardiff experiences are wholly contradictory to the findings of the Subcommittee of the British Medical Association which considers that the disease in industrial towns is essentially one of children living in damp rooms.)

Dietetic Aspects of Rheumatism in Children. C. Wilfred Vining (Address at the Bath Conference on Rheumatic Diseases, May 11, 1928).

As the result of investigations carried out in Leeds, Vining thinks that his views that the frank rheumatic child is a child suffering from toxic debility with added rheumatic infection have been confirmed. The "toxic debility" child presents the symptoms of nervous instability, limb pains, headache, listlessness and anemia. In Leeds 25 per cent of the child population from the social sphere in which rheumatism usually comes show these phenomena in greater or less degree. The "toxic debility" children exhibit certain intestinal symptoms associated with mucus and membranous material in the stools. The actually rheumatic children suffer the same way. Vining is impressed with the similiarity of the symptoms shown by "toxic debility" children and those of McCarrison's monkeys and pigeons fed on diets insufficient in vitamin B. He believes

that a dietetic theory explains why rheumatism does not appear until 4 or 5 years of age—that is to say, the dietetic deficiency takes some years to break down the defense. The family incidence of both toxic debility and rheumatism may be easily explained by the family diet. In Leeds nothing was found to support the belief that dampness plays an important part in exciting the rheumatic infection to activity. Further, in Holland where enlarged tonsils and adenoids are extremely common among school children, chorea, joint rheumatism and cardiac are rare. Vining concluded that most children who develop clinical rheumatism have a previous defective health history for months or years, which is brought about by prolonged dietetic deficiency, either in vitamin B or in protein with excess of carbohydrate, or possibly by both these factors. If this view is correct, we shall not prevent rheumatism in children by concentrating on damp houses and the removal of tonsils and adenoids, but rather by the provision of a well-balanced diet from infancy onwards. He would not rule out the possible effect of damp houses nor deny that the tonsils may be the portal of entry, but he would maintain that an exclusive throat etiology is not warranted by the evidence at our disposal.

Endocrine Factor in Rheumatism. W. Langdon Brown (Bath Congress on Rheumatic Diseases, May 11, 1928).

In dealing with the endocrine factor in rheumatism Brown thinks we may confine our attention to the ovaries and thyroid, the latter especially. He agreed with the pioneer Hertoghe that it was most important to look for evidences of hypothyroidism. Thyroid instability is the important thing, and it is possible also that spurts of hyperthyroidism on a background of hypothyroidism might be present in some cases. Lack of iodine is a feature in both, and iodine is useful both for goiter and rheumatism. Tonsillar sepsis may often be associated with thyroid derangement. It is possible that studies of the blood-sugar in rheumatism may throw some light on the endocrine factor. Insulin might be useful for rheumatic hyperpyrexia. Thyroid inadequacy may be the inherited factor in rheumatism, and at puberty and at the menopause the ovaries might act through the thyroid. Nevertheless, the thyroid and the tonsils are not the whole story in rheumatism—they are only factors. As far as endocrine factors are concerned the thyroid is the chief one in rheumatism and rheumatoid affections. There must be, however, no undue stressing of the endocrine and metabolic factors; the infective theory of the diseases takes first place.

Effect of Ash of Liver on Blood Regeneration in Pernicious Anemia. By C. A. Elden and W. S. McCann (Proc. Soc. of Exper. Biol. and Med., June, 1928, p. 746).

Observations were made of the effect of ash of liver on blood regeneration in 3 cases of typical pernicious anemia. In two cases the administration of ash of liver resulted in the appearance of some of the preliminary phenomena of a remission, in particular an increase in the percentage of reticulocytes. In neither case did a true remission occur until Minot's liver extract 343 was given. The third patient with pernicious anemia received the soluble salts of the liver ash for a period of a week. There was no evidence of any activity of the bone-marrow observed, either in the total blood count and hemoglobin and leucocytes or in the percentage of reticulocytes. In the case of the two patients showing preliminary phenomena of remission, the beginning regeneration began to diminish as soon as the soluble salts of the liver ash were given; apparently the substance responsible for the beginning regeneration was lost or inactivated by dissolving the ash in hydrochloric acid, neutralizing with NaOH and evaporating the salts to dryness.

Introduction of Iodized Oil into Respiratory Tract of Dog. W. E. Sullivan, K. F. Friedbacher, E. McKinley (Proc. Soc. of Exper. Biol. and Med., June, 1928, p. 751).

While the introduction of substances opaque to the X-ray was begun as early as 1905, it was not until the work of Sicard and Forrestier in 1921 that the practice

became general. They used a chemical combination of iodine and poppy-seed soil which is called lipiodol, and this is now in general use in diagnosis and in limited use in therapy. The question as to possible pathological changes in the lungs due to its use has never been wholly satisfactorily worked out experimentally. These investigators have carried out experiments along this line during the last two years. In one group the dogs were given 2 cc. per kilo body weight and repeated when their urine became iodine free. This period varied from 23-67 days. Four dogs were used in this group. In the remaining dogs the treatment was empirical as is often the case in the clinic. Five small dogs averaging about 8 kilos were selected and the oil introduced at convenient periods. In the first group iodine tests of the urine were made regularly, as were also differential blood counts. While an occasional animal lost in weight their health on the whole was excellent. The greatest amount of oil given any one dog was 75 cc.; the longest period that any dog was under observation was 205 days. At autopsy the lungs were studied in detail with the assistance of the Department of Pathology. Some attention was given to the other organs, especially the kidneys and spleen. The gross findings as a whole were negative. The microscopic examination in some cases showed a small amount of fibrosis and localized area of chronic passive congestion. This agrees with the recently reported observations by Pinkerton on the use of various oils in diagnosis, who found that one dose of iodized poppy-seed oil produced practically no reaction.

Cardiovascular Findings in Women with Syphilis. By JOHN H. ARNETT (Amer. Jour. of Med. Sc., July, 1928, p. 65).

Two hundred and five female dispensary patients with tertiary syphilis, 25 with secondary syphilis and 78 controls were subjected to a uniform examination, including, where possible, an electrocardiogram and an orthodiagram. The following results were obtained: Cardiac enlargement as indicated by a cardiothoracic ratio of 50 or over was present in a considerable number of the control group, as well as in both the primary and secondary syphilitic groups. No evidence was furnished for the belief that in the absence of definite evidences of cardiac impairment, syphilis *per se* may produce cardiac enlargement. On the contrary, unexplained high cardiothoracic ratios were found with approximately the same frequency in the controls as in the tertiary syphilitic group, and more rarely in the secondary syphilis group. In 3.2 per cent of the tertiary group the findings were deemed sufficient to warrant making the diagnosis of aortitis, and in 2 per cent aortic regurgitation. Arterial hypertension, both systolic and diastolic, was slightly more common in the tertiary syphilis group than in the controls. A somewhat greater frequency of arterial hypotension was found in the secondary syphilis than in either of the other two groups. Decided deviations from the normal electrocardiogram were shown more frequently in the tertiary syphilis group than in the controls, *T*-wave defects being the commonest abnormality noted. In several cases no other evidence of cardiac involvement could be found. The incidence of hypertension and cardiac enlargement increased rapidly with increasing age. Aortitis and aortic regurgitation were also more frequent in the older patients. Systolic murmurs were frequently noted both in the control and the syphilitic groups. Excluding 3 cases of aortitis from consideration, aortic systolic murmurs were no more frequent in the two syphilitic groups considered together than in the control group. Tachycardia at rest and two minutes after exercise was more common in both the secondary and tertiary syphilis groups than among the controls. Organic cardiovascular disease was not demonstrably present in any of the 25 secondary syphilis patients studied. No case of aneurism was found. Spirochetes were carefully searched for but not found in the myocardia of 2 cases of syphilis which came to autopsy during the early stage of the disease.

Reviews

Forensic Medicine. A Textbook for Students and Practitioners. By SYDNEY SMITH, M.D., (Edin.), D.P.H., Regius Professor of Forensic Medicine, University of Edinburgh; Formerly Principal Medico-Legal Expert and Director of Medico-Legal Section Egyptian Government Service and Professor of Forensic Medicine, University of Egypt; Formerly Medical Officer of Health, Department of Public Health, New Zealand, and Examiner in Public Health to the University of New Zealand. With Introduction by Prof. Harvey Littlejohn, F.R.C.S. (Edin.), F.R.S.E., Late Professor of Forensic Medicine, University of Edinburgh. Second Edition, 602 pages, 166 illustrations. P. Blakiston's Son and Co., Philadelphia, 1928. Price in cloth, $8.00.

The first edition of this work was published only three years ago, and the present one has been thoroughly revised. A number of new cases of general interest have been added, and the number of illustrations increased by about fifty, and it is hoped that the latter will greatly facilitate the study of the subject. The section dealing with the examination of fire-arms and projectiles has been enlarged and re-illustrated and part of the material dealing with this important subject has been transferred from the appendix to the general section on fire-arm wounds. The results of recent advances in many lines of work have been incorporated in this edition. Nearly one hundred pages additional material have been made necessary because of recent changes in Statutes bearing upon the subject of forensic medicine. This textbook has been written to meet the demand for a well-illustrated and concise manual of Forensic Medicine for students and practitioners. At the present time there exist very few textbooks in English upon this important field; and most of these, such as Peterson and Haines and Draper's date back to the nineties. The American textbooks have not been revised to meet the present day requirements, and the physician in America who finds himself concerned in a medico-legal testimony is hard put to find helpful reading matter on the subject. The available textbooks he finds in the library accessible to him are almost certain to be out of date. It is also a fact that in medico-legal trials the average lawyer uses as authority only these old books. The great majority of the earlier writers on forensic medicine are dead, and the posthumous editions of any textbook are usually most unsatisfactory. A new textbook on forensic medicine by a living teacher of wide experience is therefore especially timely and welcome. Sydney Smith is eminently qualified to deal with this subject. There is only one path to the mastery of Forensic Medicine, and that is an extensive practical experience acquired by a daily whole-time application and study of the medical problems which are presented by the crimes of a large community. Sydney Smith has had a unique experience in Cairo where the crimes of East and West meet in the large and cosmopolitan population of that city, which has been called the most wicked of the world. One has only to visit Cairo in order to recognize that the wealth of medico-legal work there exceeds that of any European center. In the utilization of this material Sydney Smith has developed an Institute in this branch of medicine similar to those of Vienna and Berlin, and his Institute has become the center of a wide area outside of Egypt, including the Sudan and Palestine. The author has used his extensive experience as the foundation material of this book, and his views and conclusions based upon this constitute a valuable con-

tribution to the literature of forensic medicine. He has amplified the results of his own personal experience with an analytical survey of the world's literature bearing upon the individual subjects treated, so that the volume is not simply a recital of personal experiences, but embraces a wide survey of our knowledge along this line. The treatment of these subjects is well-organized; the style is simple, concise and clear, and the illustrations add valuable information. The size of the book is convenient for the uses of the student; and the medical student will find this volume of very great help in organizing his knowledge of legal medicine.

A Textbook of Medicine. By American Authors. Edited by RUSSELL L. CECIL, A.B., M.D., Assistant Professor of Clinical Medicine in Cornell University; Assistant Visiting Physician to Bellevue Hospital, New York City; Associated Editor for Diseases of the Nervous System, FOSTER KENNEDEY, M.D., F.R.S.E., Professor of Neurology in Cornell University; Head of Neurological Department, Bellevue Hospital, New York City. Octavo of 1,500 pages, illustrated. W. B. Saunders Company, Philadelphia and London, 1927. Price in cloth, $9.00.

There are 130 contributors to the make-up of this textbook on Medicine. Most of these contributors are teachers of medicine in University Medical Schools, and the list contains many well-known names among the older internists of this country, and a goodly sprinkling of the younger generation. The rapid growth of medical science during the last few years has made it almost impossible for a single individual to master the entire field. Specialism has necessarily split up the field of internal medicine into cardiologists, gastro-enterologists, specialists in diseases of the chest, kidneys, etc., and it requires a life-time to develop each of these special fields in a thorough way. The editor has compiled a textbook of medicine in which each disease, or group of diseases, would be discussed by a writer particularly interested in that subject, and who is a student or investigator of the subject upon which he has written. This would undoubtedly have read much better and would have achieved very much better results if instead it had been "by a writer having expert knowledge of the given subject." This would have meant then that the contributors would have been composed of men having had much experience in the given line, and qualified to speak as experts, and, therefore, of necessity would have been on an average much older men than the list of contributors shows. That would be an ideal textbook of medicine, as far as this plan of individual contributors is concerned. In the first place it would be difficult in this country to get experts of this type to contribute to a textbook; such a plan was possible in the Germany of twenty years ago and still possible there in a lesser degree of efficiency and successful attainment. In this country it is practically impossible to create a thoroughly successful book on this plan, because so many of the subjects will be turned over to investigators in a given line who have no broad knowledge of the field they are working in, but are concerned only with their own personal investigations. The result is an article or chapter written with a personal bias, which may, after all, be a wholly mistaken one. Take, for instance, the subject of Yellow Fever, assigned to Noguchi and written by him wholly from the standpoint of the organism *Leptospira icteroides* as the cause of this disease. According to Agramonte and other yellow fever experts, there is not the slightest evidence that yellow fever is actually caused by this organism, and all through the world there are various investigators holding that this organism is identical with *L. icterohemorrhagiae*. From the standpoint of these workers, then, and those who have followed this work, this chapter on Yellow Fever is incorrect and misleading. This is not the only example of such "expert" contribution in this volume. In a textbook which is intended to be the final sources of knowledge on the given subject it would be much safer to have the articles written by men of largest clinical experi-

ence and knowledge than by experimental investigators in an individual line, who are more or less biased in their views, and lack the broader perspective necessary to a textbook. This criticism does not by any means apply to all of the articles in Cecil's textbook. Some of them are based on the broadest foundations and represent the subject from all necessary angles in a scientific manner. The conciseness of treatment and the condensation of material makes this textbook a popular one for students, and because of this it is the more unfortunate that many of its chapters are not more scientific and less narrowly personal. Medical knowledge is not yet in such an advanced state that every subject can be treated in a dogmatic manner; arguments on both sides must still be heard. It is difficult to do that today in the confines of a single volume, and perhaps there should be no attempt to do this, as the results, as shown in this volume, are not wholly satisfactory. There is too great an unevenness in the individual sections. In spite of its many excellencies this textbook is a glorified manual or handbook, appealing to students for its conciseness and brevity, but in too many spots not scientifically accurate.

Recent Advances in Hematology. By A. Piney, M.D., Ch.B.(Birm.); M.R.C.P. (Lond.) Research Pathologist, Cancer Hospital, London; late Director of the Charing Cross Hospital Institute of Pathology, London. Sometime Lecturer in Pathological Histology in the University of Birmingham. Second Edition. 318 pages, 4 colored plates and 18 figures. P. Blakiston's Son and Co., Philadelphia, 1928. Price in cloth, $3.00.

A new edition of this little book was required in less than a year from the time of its first appearance. The author states in the preface to this edition that a number of additions will be found in every chapter and that the section on "The Spleen in Various Infections" is entirely new. He has tried, whenever possible, to make use of the criticisms of the first edition, but in some cases states that he has followed his own views impenitently. He has aimed to include only purely morphological considerations, and not to include serology or immunology. He has intentionally ignored the subject of hemoglobin, as the recent advances in our knowledge of this subject are mainly biochemical and outside the scope of this book. To the American reader this book seems somewhat behind the times, particularly in the discussions on pernicious anemia, the neoplastic theory of Hodgkin's and the lymphoblastomas, etc. The word reticulocyte does not appear in the index, and the regenerative changes in the blood under liver diet in pernicious anemia are not mentioned. Ayerza's disease is not discussed, and there are numerous other omissions that come under the head of hematology. There are few new essentials in the material of this book differing from that of the first edition.

Cardiac Arrhythmias. Clinical Features and Mechanism of the Irregular Heart. By Irving R. Roth, M.D., Assistant in Medicine; Chief, Children's Cardiac Clinic, Mt. Sinai Hospital; Instructor in Post-Graduate Studies on Diseases of the Circulatory System Conducted by Columbia University at Mt. Sinai Hospital, N. Y. Introduction by Emanuel Libman, M.D., Clinical Professor of Medicine, Columbia University. 210 pages, 80 illustrations and 5 tables. Paul B. Hoeber, Inc., New York, 1928. Price in cloth, $7.50.

The author has aimed in this volume to present in simple diagrammatic form the mechanism of the various types of cardiac irregularity together with their clinical signs, such as electrical manifestations, heart sounds and the arterial and venous pulses. The diagrams are drawn to scale in order that the various components of the extracardiac manifestations of the heartbeat may be correlated with one another and with the corresponding phases of the intrinsic cardiac mechanisms in any given arrhythmia. The attempt is made to simplify by aid of diagrams the understanding of that intrinsic disturbance in the cardiac

mechanisms known as "circus movement" which is accepted today as the underlying disturbance of rhythm in clinical auricular flutter and fibrillation. Text matter has been reduced to a minimum! it is a simple, clear text sufficient to make the mechanism and significance of the arrhythmias more easily understandable by the uninitiated. The diagrammatic representations of the mechanism of auricular flutter and fibrillation are original and striking. The first part of the book deals with normal anatomical and physiologic facts and phenomena. The second part deals with the arrhythmias exclusively. Clinical signs and symptoms are stressed throughout the volume. The author hopes that his book will awaken a wider interest in the bedside study of the irregular heart. It should be of great value to the general clinician in its presentation of the elements of graphic studies in the arrhythmias and the emphasis of their clinical features. The volume is handsomely printed, and the illustrations beautifully reproduced. To any one who does not feel sure of his understanding of the mechanism of the heart beat this book can be warmly recommended.

Special Cytology. The Form and Functions of the Cell in Health and Disease. A Textbook for Students of Biology and Medicine. Edited by EDMUND V. COWDRY. 2 volumes, large octavo, 1,376 pages, 693 illustrations. Paul B. Hoeber, Inc., New York, 1928. Bound in waterproof sturdite, $20.00.

This is a composite work to which some 33 writers have contributed sections along lines of cytology in which they have been personally more or less interested. The different kinds of cells which make up the human body—blood cells, nerve cells, gland cells, etc.—are treated individually in the separate sections. These contributors are chiefly anatomists. The book is to be regarded as supplementary to an earlier volume called "General Cytology" published by the University of Chicago Press in 1924, and now in its second printing. In that volume the fundamental principles of architecture and activity which cells of different kinds possess in common were discussed by a group of workers chiefly recruited from the biological sciences; the purpose of this book is to present a detailed statement of the types of cells which make up the body, and which serve different functions, including both physiologic and pathologic conditions. These conditions as they appear in the adult are stressed; very little embryology is given. Known facts are given, and the probable explanations, and suggestions as to the possible line of advance. Methods of technique are treated only superficially, as it is proposed to publish a cooperative book on "Cytological Technique". Leading references to the literature are cited at the end of each section. The individual writers have at their own discretion utilized the literature at their own valuation, and instead of a mechanical review based upon abstracts of each research that has appeared on a given subject we see the literature through a personal selection and interpretation of the compiler rather than of the original author. Although the title page includes the form and functions of the cell in disease as well as in health, pathologic cytology is really given but little attention. The volume is essentially histologic, and the pathologic descriptions and interpretations very incomplete and inadequate. The articles, however, are very uneven in this respect. The chief value of the book is its encyclopedic collection and arrangement of the chief facts known concerning the cells of the various tissues and organs included in this treatment. To such an assemblage of cytological information it will be convenient for the laboratory worker to turn when he needs to refresh his memory as to some cytological fact or investigation. Such a compilation should have been prepared without any possibility of personal bias as to cytological conceptions, but in several places such personal views seem to appear. The book is well printed, but the reproductions of the illustrations are very uneven, due, no doubt, to the difference in style and quality of the originals. In spite of certain imperfections the two volumes will be indispensable to the working laboratory library.

College News Notes

Dr. Samuel S. Berger (Fellow), Cleveland, Ohio, is now Internist in Charge of the Medical Service of Mt. Sinai Hospital, Cleveland.

Dr. L. T. LeWald (Fellow), Professor of Roentgenology, New York University, is scheduled to read a paper at the Second National Congress of Radiology at Stockholm on July 25, 1928. The subject of the paper is: "Diaphragmatic Hernia: Differentiation from Thoracic Stomach, Absence of the Left Half of the Diaphragm, and Eventration of the Diaphragm."

Dr. Carl V. Vischer (Fellow), Philadelphia, Pa., presented a paper on "Ultra Violet Ray in the Treatment of Pulmonary Tuberculosis" with case reports, at the meeting of the National Society of Physical Therapeutics at Pittsburgh on June 21.

Dr. G. Harlan Wells (Fellow), Philadelphia, Pa., recently completed a successful year as President of the American Institute of Homeopathy. The annual meeting of the Institute was held at Pittsburg, Pa.. June 17-21, 1928.

Dr. Karl Rothschild (Associate), New Brunswick, N. J., recently addressed the staff of the Middlesex General Hospital, presenting reports with post-mortem notes on two cases, one of acute infectious myelitis (encephalo-myelitis) and one of acute yellow atrophy of the liver, probably due to arsphenamine poisoning.

Dr. Rothschild also addressed the Middlesex County Medical Society on the subject of Huntington's Chorea and the Corpus Striatum Syndrome, with demonstrations of family trees and photographs, on June 20.

Dr. E. Roland Snader, Jr. (Fellow), Philadelphia, Pa., read a paper at the annual meeting of the American Institute of Homeopathy at Pittsburgh, Pa., entitled: "Diagnosis of Renal Diabetes," with case reports.

Dr. Carl V. Vischer (Fellow), Philadelphia, Pa., was recently appointed Director of the Department of Physical Therapeutics of St. Luke's Hospital of Philadelphia.

Dr. Donald R. Ferguson (Associate), Philadelphia, Pa., read a paper entitled: "Clinical Aspect of Massive Collapse of the Lung," (illustrated) before the annual meeting of the American Institute of Homeopathy at Pittsburgh, Pa., on June 20.

Dr. H. M. McClanahan (Fellow), Omaha, Nebr., is the author of a new book on "Pediatrics for the General Practitioner."

Dr. W. G. Gamble, Jr. (Asociate), Lecturer in Clinical Pathology, Medical College of South Carolina, Charleston, has been appointed as Instructor in Pathology also. Dr. Gamble and wife attended the meeting of the American Medical Association at Minneapolis in June where he presented a paper entitled, "The Young Clinical Pathologist," dealing with the acute lack of Pathologists in this country, before the American Society of Clinical Pathologists. Mrs. Gamble represented the South Carolina Auxiliary at the national meeting of the Auxiliary to the American Medical Association.

Dr. Sidney K. Simon (Fellow), New Orleans, La., has been elected president of the New Orleans Gastro-Enterological Society for the present year.

Dr. James Birney Guthrie (Fellow), New Orleans, La., is President of the Orleans Parish Medical Society.

Dr. John B. Youmans (Fellow) has been appointed Associate Professor of Medicine at Vanderbilt University School of Medicine, Nashville, Tenn.

Dr. George H. Whipple (Fellow), Rochester, N. Y., was elected Vice-President, and Dr. Howard T. Karsner (Fellow), Cleveland, Ohio, was elected Secretary, of the American Association of Pathologists and Bacteriologists at their last annual meeting at Washington, D. C. The President of this Association, Dr. Edward B. Krumbhaar, Philadelphia, is also a Fellow of the American College of Physicians.

Under the presidency of Dr. Lewellys F. Barker (Fellow), Baltimore, Md., the Inter-State Post Graduate Association of North America will meet at Atlanta, Ga., October 15-19.

Dr. Henry O. Colcomb (Associate), has recently been appointed Assistant in Neuro--psychiatry at St. Elizabeth's Hospital, Washington, D. C. Formerly, Dr. Colcomb was located at National Soldiers Home, Va.

Dr. Edwin C. Ernst (Fellow), St. Louis, Mo., is President of the Radiological Society of North America. He was also recently elected to the Board of Chancellors of the American College of Radiology.

Dr. Maximilian J. Hubeny (Fellow), Chicago, Ill., just retired from the Presidency of the American College of Radiology. Dr. Hubeny is now the President Elect of the Radiological Society of North America, and was recently elected Chairman of the Section for Radiology of the American Medical Association.

The American College of Radiology has a limited membership of one hundred Fellows, made up of men who have distinguished themselves in Radiology. Dr. Alfred L. Gray (Fellow), Richmond, Va., is President; Dr. Albert Soiland (Fellow), Los Angeles, Calif., is Executive Secretary; Dr. B. H. Orndoff (Fellow), Chicago, Ill., is Treasurer; Dr. I. S. Trostler (Fellow), Chicago, Ill., is Historian; Drs. E. C. Ernst, St. Louis, Mo., F. A. Groover, Washington, D. C., G. E. Pfahler, Philadelphia, Pa., and R. H. Stevens, Detroit, Mich., are on the Board of Chancellors.

Dr. I. S. Trostler (Fellow), Chicago, Ill., was made the recipient of a gold medal as a "token of service" at the meeting of the Radiological Society of North America in New Orleans last winter.

Dr. Carl V. Weller has been reelected Secretary of the American Society for Experimental Pathology. For the ensuing year this carries with this office that of General Secretary of the Federation of American Societies for Experimental Biology. In the Journal of the American Dental Asociation for June there appears an article by Dr. Weller on Constitutional Factors in Periodontitis.

Dr. Aaron E. Parsonnet (Fellow), Newark, N. J., has presented to The College Library the following reprints of work at the Newark Beth Israel Hospital, by himself and his associates during the present year:

Abdominal Manifestations in Cardiovascular Disease

Electrocardiographic Control of Active Digitalization in Auricular Fibrillation

Quinidin Therapy; Uses and Contraindications in Auricular Fibrillation.

Dr. Thomas G. Simonton (Associate), Pittsburgh, Pa., President-elect of the Medical Society of the State of Pennsylvania, addressed the Northampton County Medical Society, June 15, on "Pleurisy with Effusion and Referred Chest Pains."

Dr. Oscar W. Bethea (Fellow), Professor of Clinical Medicine and Therapeutics, Tulane University School of Medicine, is author of a new book on Clinical Medicine, published by W. B. Saunders Company.

Dr. William A. White (Fellow), Medical Superintendent of St. Elizabeth's Hospital, Washington, D. C., recently addressed the New England Society of Psychiatry at Providence on "Contribution of Psychiatry to the Problem of Crime."

Dr. Ada E. Schweitzer (Fellow), Indianapolis, Ind., delivered the annual Chautauqua lecture at the Winona Lake Chautauqua Child Health Week, July 9-13, entitled, "The Child and His World."

Dr. Henry Daspit (Fellow), New Orleans, La., has been appointed Dean of the Graduate School of Medicine, Tulane University of Louisiana, to take office at the end of the fiscal year, September 1928.